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THE TREATMENT OF ATOPIC ECZEMA WITH SYSTEMIC STEROIDS.*

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THIS is an account of the treatment of a group of sufferers from severe atopic eczema with continuous systemic steroids. The first reports in this country on the use of steroids in the control of "Besnier's Prurigo", such as those of the M.R.C. Panel (1954) and Dowling (1953), were not at all encouraging. Both accounts were emphatic that treatment with A.C.T.H. or cortisone, even if it lessened symptoms during its use, was promptly followed by relapse which might leave the patient worse than before when the drugs were discontinued.

Across the Atlantic in 1956, Johnson and Cazort stated that prednisolone should only be used as a last resort measure in atopic eczema and Sulzberger (1956) set out ten warning rules for the use of steroids, though he admitted it was justifiable in some cases of atopic eczema.

But by 1957, Bukantz and Aubuchon had treated 113 adults with allergic disease with prednisolone, 15 of them for more than six months, without dire results. In 1958, Arbesman and Ehrenreich described six patients who had been maintained for more than five years on continuous steroid suppression but one had developed hypertension and albuminuria, though these were not thought necessarily the result of treatment.

Wells (1958) stated that steroids were seldom justifiable and only required if life were insupportable outside hospital. Although many dermatologists pay lip service to this ideal, it is felt that steroids are used quite widely in

* Based on a paper read at a symposium on steroid therapy at the Thirty-ninth Annual Meeting of the British Association of Dermatology in July 1959.

atopic eczema though little has been published on the subject in this country in the last few years. It certainly appears that treatment may have to be maintained for long periods to be successful, but the ultimate fate of such treated patients is unknown. It is recognised that as far as the eczema is concerned, these patients have a normal expectation of life and their disability lessens with age. Although Stephen Rothman has said that eczema does not end life, it completely ruins it, any treatment which shortens the life span is unjustifiable.

INVESTIGATION.

Two years ago, having reviewed the results of continuous steroid treatment in pemphigus and pemphigoid and in one or two very severe cases of eczema, it appeared to me that the dangers had perhaps been somewhat exaggerated and I decided to select a few of the most disabled patients with extensive atopic eczema and attempt to control their symptoms with steroids. The introduction of prednisolone with the lessened risk of salt retention, encouraged this plan.

The first cases chosen were those adults who by reason of their complaint were unable to earn their livings or had to spend a large part of their lives in hospital and whose symptoms had not responded to the liberal use of topical steroids and other more conventional methods of treatment, including psychotherapy. Adults were selected as it was considered there would be no difficulty over alteration in growth and they would be less likely to put on weight excessively. No case was treated unless the patient had a normal chest x-ray and had no history of peptic ulceration and no hypertension. Many of the patients had been observed for periods of ten years before the steroids were used and therefore no controlled trial with dummy tablets was carried out. In view of the risks of sudden cessation of steroid therapy, no dummy tablets were substituted once treatment had started. However, even a slight reduction in dose led to such a marked relapse in the objective findings that it was felt that any improvement was due to the treatment and not to the new treatment syndrome.

Up to the present, 26 patients with severe and intractable atopic eczema have been treated with continuous steroids for 4 months to $4\frac{1}{2}$ years. These cases were drawn from approximately 500 of atopic eczema seen in ten years. Thirteen were men and 13 women. Ten had other allergic disease and 16 had a family history of eczema, asthma or hay fever. Fourteen had had eczema since infancy. Six suffered in infancy, the eczema clearing but recurring after puberty and becoming a problem in the late teens. Six developed the disease after puberty but the majority of these had suffered for over ten years before receiving treatment with steroids.

Clinically, there was no visible difference between the patients in the groups with the different histories. A point which I have not fully realized before is that some of the most intractable cases start in the late teens. Many begin with itching and scaling of the scalp and are difficult to differentiate from seborrhoeic dermatitis at the onset. The progress of the disease is to involve the face, sides of the neck, upper chest and the antecubital fossae, and the association with asthma and hay fever either in the patients themselves or their close relatives, serves to differentiate it from seborrhoeic eruptions, as does the intensity of the itching. This severe eczema in the late teens causes a maximum disruption of the patients' lives, since in

men it interferes with their careers and in girls it produces severe depression because of the unsightliness of the skin lesions.

The age distribution of the cases treated with steroids is shown in Fig. 1. The oldest patient was aged 65 and had never been free from symptoms. He had

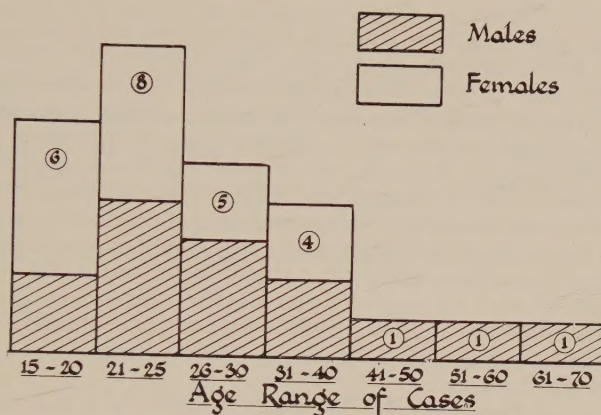


FIG. 1.

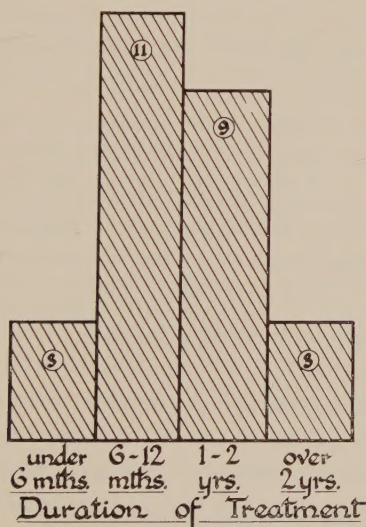


FIG. 2.

become even more disabled in the two years before treatment started, developing into almost an exfoliative dermatitis.

The duration of treatment is shown in Fig. 2. Prednisolone was used in 13 cases, dexamethasone in 6: combinations of cortisone, prednisolone, Ledercort and dexamethasone were employed in 7.

RESULTS.

Good control was obtained in 19 cases, fair control in 5, and 2 were failures. It is impossible to review all the cases but I will mention a few examples.

The first, a good result. A man aged 36, a sorter in the Post Office, suffered from eczema in infancy which cleared but recurred when he was 26. This became more and more disabling until it was virtually generalized. Two and a half years ago he was started on cortisone at St. Thomas's Hospital, London, and nine months later he moved to Sheffield, still on cortisone. By this time he was much improved, but he still had lichenification of the neck and antecubital fossae, popliteal spaces and thighs. Three months later, I changed his treatment to prednisolone 5 mg. 4 times a day. He has been maintained on prednisolone and is now on a maintenance dose of 5 mg. 3 times a day. He is virtually clear of any skin change except pigmentation. Much of the lichenification has vanished. He is now a successful insurance agent and has had no time off work for over eighteen months. On two occasions he has had slight relapses controlled by temporary increases of steroids. He shows a little facial fattening but has gained only two to three pounds in weight and his blood pressure has remained the same.

The next case was a man aged 45 who was a labourer in a steel works. He had eczema in infancy and from the age of 25 onwards eczema together with asthma. His two sisters had asthma. He was repeatedly in hospital in 1957 and was off work for 6 months and again for 8 months in 1958. He had extensive eczema of the face, neck, legs, arms and head with lichenification and some exudation and secondary infection. Prednisolone 10 mg. 3 times a day was started fourteen months ago. Since then he has worked regularly and is now on prednisolone 5 mg. 3 times a day. He uses a little hydrocortisone ointment on the face and no local treatment elsewhere. He has gained one stone in weight and has a moon face but no other side effects. His blood pressure is not raised.

There have been two poor results, one in a man of 27 who started with eczema at the age of 14. His father also had eczema and asthma. He was completely incapacitated and had been in hospital for much of his life until 1953 when steroid treatment was started. He has been somewhat improved but the condition has not been completely controlled, even with high doses. He has worked regularly whilst on steroids until recently when despite prednisolone and more recently Ledercort in a dose of 4 mg. 3 times a day, he developed an exfoliative dermatitis. He was perhaps the most severe of the cases and it is apparent that there are examples where even a heavy dose of steroids does not control the condition.

Some of the other patients, though improved, certainly mentally, have not been free from itching or the need for some local applications. It has been interesting to observe how the dosage necessary to keep the disease under control has varied. An intercurrent disease such as influenza has in some cases produced a flare up which has necessitated a temporary increase in dose. Occasional severe emotional disturbances appear to have done the same.

One of the most striking features has been the change in the personality of the patients who have altered from miserable, tense depressives to extraverted, cheerful individuals, far more fitted to cope with life. I feel that insufficient attention has been given in the past to the effect of the skin disease on the psyche. Three of the patients I have treated attempted suicide before

treatment and so far, none has had another try. Serious side effects have not occurred and no case has had to give up treatment. In particular, no case has developed hypertension, glycosuria or osteoporosis. Gain in weight and moon face have been very common and I now warn patients that their skin rash can be improved only at the expense of putting on weight. A possible explanation as to why there has been so little trouble with side effects is that the eczema patients are otherwise normal healthy people who are up and about and the graver side effects occur in those patients who are severely damaged by disease such as rheumatoid arthritis and in cases that are bedridden. One anxiety always present is the risk of a surgical emergency and every patient carries a warning card to show if he should have to consult a surgeon. The risk of adrenal failure during surgery would seem the greatest hazard that these patients face.

Another problem is pregnancy. Three of the young girls on treatment have married since their eczema has been controlled and one other married woman has produced a normal child. Fortunately I was able to discontinue the steroids after the first missed period and treatment was not restarted until after the twentieth week, when the eczema was so bad that it became necessary to resume treatment. There have been reports of patients' producing normal children despite steroids throughout pregnancy but obviously this is a risk which should be avoided.

No difference between the results of treatment with dexamethasone and prednisolone was noticed; as prednisolone is relatively cheaper there would appear to be no advantage in using the newer preparation. In the few cases where triamcinolone was used, more dyspepsia occurred than in the others and in view of untoward happenings in cases not in this series, it was not used very much. Most cases are down to a maintenance dose of prednisolone of 5 mg. 3 times a day or less. Some can manage on only one 5 mg. tablet a day though if this is discontinued, their skin rash recurs. With dexamethasone, the dosage has to be slightly higher: it appears that 0.5 mg. 4 times a day is comparable in effect with prednisolone 5 mg. 3 times a day. How long treatment will have to be maintained, remains to be seen. If other conditions such as pemphigus can be taken as an example, it may be possible to lower the dose still further over a longer period and discontinue it altogether in some cases. Only one of this series has discontinued treatment and remained well.

What damage has been done to the patients is also unknown. It is intended to investigate in the future how much adrenal activity is left after several years on a small maintenance dose of steroids. Whether any lasting harm has been done it is as yet impossible to say. I believe that in the worst cases of atopic eczema, who are unable to live reasonable lives, continuous steroid therapy is effective in the large majority at the expense of changing their contours and of constant vigilance to see that they do not run into difficulties.

I do not think that the treatment should be started unless close observation is possible as it must be realized that if steroid treatment is started, it will have to be maintained for a long time.

SUMMARY.

An account is given of continuous steroid treatment in 26 adults (13 men and 13 women) suffering from severe atopic eczema. Treatment has been maintained for periods of 4 months to $4\frac{1}{2}$ years. Control of symptoms has been good in 19, fair in 5 and poor in 2. No difference in efficacy has been noted between dexamethasone and prednisolone. Final maintenance doses have been in the region of 10–15 mg. of prednisolone daily. No serious side effects have been encountered but the majority of patients gained weight and developed moon face.

It is stressed that some harmful effects may yet arise and treatment should not be embarked upon lightly or in the absence of adequate facilities for close supervision.

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CORTICOSTEROID THERAPY IN BESNIER'S ECZEMA.*

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BECAUSE of its chronic and disabling character and its incidence in all strata of society, Besnier's eczema is a disease of considerable importance (Hellerström and Lidman, 1956). The difficulties which may be encountered in its treatment are well known but the advent of cortisone and the analogous steroid drugs has offered the prospect of a new method of therapy. In the literature, while some references can be found reporting beneficial effects during the use of corticosteroid drugs in this particular condition, numerous publications on other subjects have drawn attention to possible harmful side effects.

This small survey of cases of Besnier's eczema records the clinical response to prolonged systemic administration of corticosteroid drugs in 23 patients, the side effects encountered and the clinical result of stopping such therapy.

All the patients suffered from Besnier's eczema of long duration, in most cases since infancy. The eldest was 57 years of age at the beginning of treatment, the youngest was 18 months: 17 patients were at the age of puberty or over, 6 patients were under the age of 10. For the most part, prednisolone was used. In the older group, dosage ranged from 5 to 15 mg. per day; the children received 2.5 to 5 mg. per day except the 18-month-old patient who never had more than 1.0 mg. daily. Apart from two patients treated for three and six months respectively the duration of the therapy ranged from eight months to over three and a half years. Most patients received this therapy for over one year. Assessment was made from both objective findings and the patient's own impressions.

Of the 23 patients under consideration, 18 showed definite improvement and 5 revealed little or no change. Among those improved, 14 recorded a diminution of pruritus and of the latter 10 slept better. In 10 cases, asthma was also present. This was alleviated in 3 and unchanged in 5, in one case an exacerbation occurred at first but subsequent benefit was obtained, in the remaining patient with asthma no change took place.

Side effects were encountered in 11 of the 23 patients during the treatment.

Gastro-intestinal tract.—Six patients experienced anorexia or dyspepsia. Two of these had frank pain which was alleviated on reduction of dosage or withdrawal of the drug.

* Based on a paper read at the Thirty-ninth Annual Meeting of the British Association of Dermatology in July 1959.

Infections.—Four patients developed intercurrent infections, namely, a chest wall abscess, urinary tract infection, sinusitis and furunculosis.

Acne vulgaris.—This occurred in three patients; one was a man aged 23 years and two were girls aged respectively 13 and 19 years. Although the onset of acne in these cases may have been coincidental, corticosteroid therapy may have contributed to it.

The diastolic blood pressure rose slightly in one patient when his dosage was increased from 10 mg. to 15 mg. per day. It fell again on reducing the dose to 10 mg. Occasional *headaches* were experienced by four patients.

Drowsiness was noted by one man, *menstrual irregularity* was encountered in one woman. *Impotence without loss of libido* occurred in a man aged 57 years.

Side effects also occurred in two patients when the therapy was discontinued. One man aged 25, whose asthma had been uninfluenced during treatment, developed either very frequent asthmatic attacks or actual status asthmaticus shortly after stopping treatment, which required his admission to another hospital. The other, aged 15 years, developed an epileptiform convulsion within two days of stopping treatment; no clear previous history of epilepsy could be obtained here. The electroencephalogram showed an episodic disturbance of *grand mal* epileptic pattern. Thus, of the 23 patients under review, 13 developed side effects either during or after therapy with steroids.

I have stated that 18 out of 23 patients showed an improvement in their skin during steroid therapy. Of those 18 patients, four received two courses of treatment. Thus, in all, 22 courses of treatment were given to this group. In 5 cases treatment continues. Therefore steroid therapy has been discontinued on 17 occasions. In 14 of these 17 instances relapses have occurred in the skin within 10 months; 2 relapsed within one week, 6 within 2 months, 2 within 3 to 6 months and 4 within 7 to 10 months. One patient has remained clear for 10 months and another for 6 months. Accurate assessment of relapse in the remaining instance has not been possible.

DISCUSSION.

Beneficial effects during the use of oral corticosteroid drugs in Besnier's eczema have previously been reported. Sulzberger and Witten (1954) recorded improvement in all 12 established cases during cortisone therapy. Bukantz and Aubuchon (1957) treated 7 children and 9 adults with prednisone or prednisolone and their patients obtained considerable relief. Rein *et al.* (1957) found marked improvement in 16 patients, and Kalz (1958) obtained satisfactory results in 24 patients treated with triamcinolone. Feinberg *et al.* (1957) gave methylprednisolone to 5 cases and reported improvement in all. That the corticosteroid group of drugs can produce improvement in Besnier's

eczema is therefore becoming well established. The dosage required is usually moderate and satisfactory control can often be effected on small maintenance doses.

The side effects during treatment reported in this paper have been relatively mild. This corresponds in general with the findings of the authors mentioned above, except that Kalz (1958) had one patient who developed radiologically confirmed reactivation of a duodenal ulcer. Although the dosage employed in the various series referred to has for the most part been moderate, it would be dangerous to assume that the use of moderate doses of corticosteroids may be attended by only minor side effects. Thus Virkunen and Lehtinen (1958), recording their observations after five years' continuous use of corticosteroid drugs in patients with rheumatoid arthritis and other rheumatic diseases, encountered more serious side effects; these included peptic ulceration, osteoporosis, vertebral fractures, pulmonary tuberculosis, hypertension, coronary occlusion and thromboembolism. Their mean daily dosage cannot be considered anything other than moderate. Moreover, prolonged administration of steroids is not always necessary before a more serious side effect can occur. For example, Brown and Haserick (1957) reported the development of a duodenal ulcer, in a patient with no previous history of the latter, only three weeks after beginning triamcinolone therapy (12-16 mg. daily) for psoriasis. Therefore, while one may be fortunate and encounter only minor side effects during corticosteroid therapy, it is obviously important to recall that, even with moderate dosage, serious side effects can occur and that at least one such side effect can occur early in a course of treatment.

While close supervision of patients under treatment with steroids is obviously necessary, the occurrence of very severe asthma in one patient and an epileptic seizure in another soon after discontinuing steroid therapy, indicates the need for close care beyond the actual period of such therapy. This is all the more important if adrenocortical function has been suppressed, which is likely (Dewar and White, 1959). The patient who developed the epileptic fit latterly received methylprednisolone instead of prednisolone. An association between the administration of methylprednisolone and the onset of convulsions has previously been reported by MacMahon and Gordon (1959).

The benefits which may be expected in treating patients who have Besnier's eczema with oral steroids, therefore, must be weighed against the possible development of side effects both during and after therapy. They must also be weighed against the development of relapses after cessation of therapy. The present investigations suggest that such relapses can be expected in a high proportion of cases. This impression confirms the observations of Goldsmith (1955) and of Sulzberger *et al.* (1958) who have emphasized the temporary "morbidistatic" nature of steroid therapy. Indeed, the physician who treats a case of Besnier's eczema with oral corticosteroids and intends to keep the

patient's skin clear, may have to continue such therapy indefinitely. Faced with this prospect, he may prefer to rely on other methods of treatment.

SUMMARY.

The results of treating 23 patients with Besnier's eczema by means of oral corticosteroids, mainly prednisolone, are recorded.

Benefit was obtained in 18 cases and in 5 there was no improvement.

Side effects were encountered in 11 patients during treatment and were mostly mild.

Side effects were encountered after treatment in 2 patients and were more serious.

Where therapy was stopped, relapses occurred in periods ranging up to 10 months in 14 out of 17 instances.

Dr. James Sommerville suggested this investigation. I would like to thank him for his interest in and criticism of the paper, and for allowing me access to the records of the patients, all of whom were under his care. I would also like to thank Dr. W. A. Dewar for his assistance in the preparation of the paper.

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TREATMENT IN BULLOUS DISEASES WITH CORTICOSTEROID DRUGS AND CORTICOTROPHIN.

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THE purpose of this paper is to review the results of treatment with corticosteroid drugs and with corticotrophin in 172 patients with bullous diseases (Table I).

TABLE I.—*Analysis of 172 Patients Treated with Corticosteroids.*

Erythema multiforme . . .	17	Pemphigus	61
Dermatitis herpetiformis . . .	10	Pemphigoid	68
Herpes gestationis	2	Benign mucous membrane pemphigoid	14

These patients attended the Skin Department of one of 10 London undergraduate Teaching Hospitals, or of St. John's Hospital for Diseases of the Skin, London. By courtesy of the physicians in charge, the case records at these hospitals over 7 years, from January 1952, to April 1959, were reviewed, a follow-up survey was made and individual cases discussed.

Of 61 patients with pemphigus, all but 4 had histological evidence of acantholysis. The latter 4 patients were severely ill and on clinical grounds the diagnosis was considered certain. Biopsy in patients with other bullous disorders had been carried out when considered necessary to support the diagnosis.

When reference is made to steroid dosage, the equivalent dose of prednisone will generally be given.* Minor side effects such as "moon face", gain in weight, glycosuria and minor degrees of oedema are ignored when complications are discussed, since they seem inevitable in a proportion of patients treated with corticosteroid drugs.

For convenience the two largest disease groups in this series (pemphigoid and pemphigus) will be reviewed last.

ERYTHEMA MULTIFORME.

Fifteen of these 17 patients gave a history of recurrent attacks, and two were classed as cases of Stevens-Johnson syndrome. There were no complications from treatment.

Individual attacks were successfully suppressed with corticosteroids given for 2-6 weeks in dosage equivalent to 20-30 mg. of prednisone daily.

* 1 mg. of prednisone	= 5 mg. of cortisone.
1 mg. of aqueous corticotrophin I.M.	= 2 mg. of cortisone.
1 mg. of corticotrophin gel I.M.	= 5 mg. of cortisone.
1 mg. of corticotrophin I.V.	= 10 mg. of cortisone.

One patient with recurrent Stevens-Johnson syndrome obtained little relief from steroid drugs once the attack was established, but obtained dramatic relief from cortisone given early in an attack. Two patients with predominantly oral lesions at first responded to short courses of treatment, but later required continuous therapy.

DERMATITIS HERPETIFORMIS (DUHRING).

Only 10 patients with this condition were given corticosteroid therapy. Five did not benefit and continued with other treatment. Four patients were maintained successfully on corticosteroid drugs, and one patient obtained most relief from a combination of prednisone and diaminodiphenyl sulphone. The only complication encountered in this group was a transient episode of diabetes. In addition, two patients with herpes gestationis from this series, described by Russell and Thorne (1957), obtained a satisfactory response to treatment and this could be withdrawn before term.

BENIGN MUCOUS MEMBRANE PEMPHIGOID.

Fourteen patients with this disorder were treated with corticosteroids and no complications occurred. Four patients showed no improvement, the maximum daily dosage of corticosteroid employed being the equivalent of 60 mg. of prednisone in two cases, 40 mg. and 20 mg. respectively in the other two. The ophthalmic aspect of one of these refractory cases was reported by Minton (1955), A.C.T.H. also being given in this case.

Seven other patients (one with active skin lesions only), responded well to the equivalent of 15 to 60 mg. of prednisone daily although in only 2 cases were the mucous membrane lesions completely suppressed and these were oral lesions. No ophthalmic lesions in the series were completely suppressed. The remaining 3 patients derived some benefit from corticosteroids given during exacerbations of the disease.

The difficulty in suppressing mucous membrane lesions with corticosteroids has also been reported by Church and Sneddon (1956), and Lortat Jacob (1958). McCarthy and Sklar (1958), who reviewed 15 patients with benign mucous membrane pemphigoid, found difficulty in suppressing all manifestations of the disease completely, and noticed that the amount of corticosteroid required to control the disease varied considerably. The resistance of four cases to treatment in the present series is significant.

PEMPHIGOID ("BULLOUS PEMPHIGOID").

Sixty-eight patients with pemphigoid were treated, aged from 44 to 93 years, the average age being 69 years. Biopsy was carried out in 52 cases and showed a subepidermal bulla without acantholysis,

TABLE II.—*Pemphigoid*—68 Patients—*Response to Treatment*.

(i) Steroids given then withdrawn	30	Later died of natural causes . . .	4
—remission followed		Not followed up . . .	1
(ii) Maintained on steroids . . .	32	Died	
		Natural causes . . .	8
		Perforated D.U. . . .	1
		Pneumonia . . .	1
		Not followed up . . .	1
(iii) Unsatisfactory response . . .	6		

Response to Treatment.

In Table II the 68 patients with pemphigoid are divided into three groups according to their response to treatment.

(i) Thirty patients received steroid therapy for a limited period and then it was withdrawn. In 23 of these, therapy was for less than one year, in 4 more it was for longer but for less than two years, while the remaining 3 patients had steroid treatment for over three years. Many of these patients who required steroid treatment for less than one year had at first been severely ill.

Remission, after therapy was stopped—complete except in 5 patients who have occasional minor lesions, has been for over three years in 11 patients and for over one year in eleven more (one of these died from pneumonia 18 months after stopping treatment). Of the remaining 8 patients one aged 84 years was not followed up, 3 died from natural causes within a year of stopping treatment and 4 have remained in remission since stopping treatment during the past year.

(ii) Thirty-two patients have been effectively treated with continuous steroid therapy, seven of these for over 4 years, eleven more for over 2 years, the remainder for less than 2 years. All but one of these 32 patients have been followed up.

The mortality in this group was 10. Eight deaths were considered to be due to natural causes (cerebral vascular accident; carcinoma of bronchus; carcinoma of pancreas occurring after 2 years of treatment; uraemia; hypertensive heart failure with pneumonia; cerebral arteriosclerosis with cardiac failure; urinary infection at the age of 93 years; hypertensive heart failure with pulmonary embolism—treatment with A.C.T.H. may have contributed to a slight degree towards the death of this 69 year old patient who also had ischaemic heart disease). The bullous eruption in the patient who had carcinoma of bronchus may have been related to the malignancy.

Two deaths could clearly be related to steroid therapy. One patient, a man of 66 years developed afebrile but fatal bronchopneumonia. The other, a man of 75 with severe buccal as well as cutaneous blisters had a high dosage of prednisone for 5 weeks. He died rapidly from peritonitis due to a perforated duodenal ulcer. He gave a previous history of dyspepsia. In both

patients the symptoms were masked and the fatal illness rendered atypical by steroid therapy. No death in this series could be attributed to pemphigoid.

(iii) Finally there remained 6 patients who did not respond satisfactorily to steroid drugs and were given alternative treatment. Four of these patients are now well and symptom-free, but cannot be traced.

Steroid Dosage.

The maximum dosage of corticosteroids in terms of prednisone required to control the most severe phase of the disease in 60 of the 62 patients with

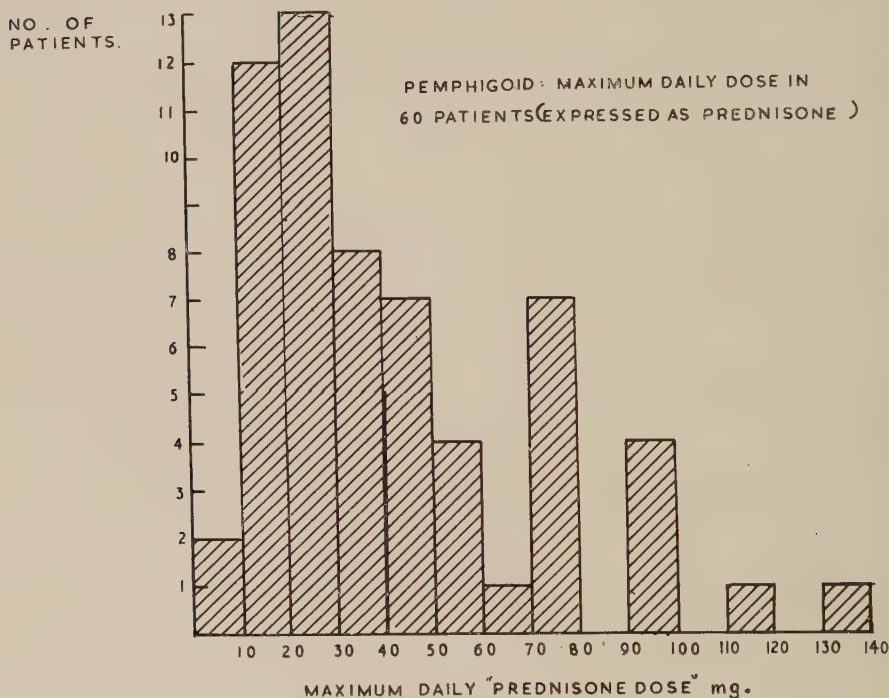


FIG. 1.

pemphigoid who responded to treatment, is shown in Fig. 1. These data were lacking in the two remaining patients who had earlier been treated at other centres. It is evident that over half of the patients required a maximum dose of 40 mg. of prednisone or less and over two-thirds of the total required 60 mg. or less. This contrasts markedly with the requirements in pemphigus which were much greater (Fig. 2). Relapses in the pemphigoid series were easily controlled in contrast to those of pemphigus cases. There was no evidence that younger patients required a higher dosage of steroids than older patients, nor of the reverse.

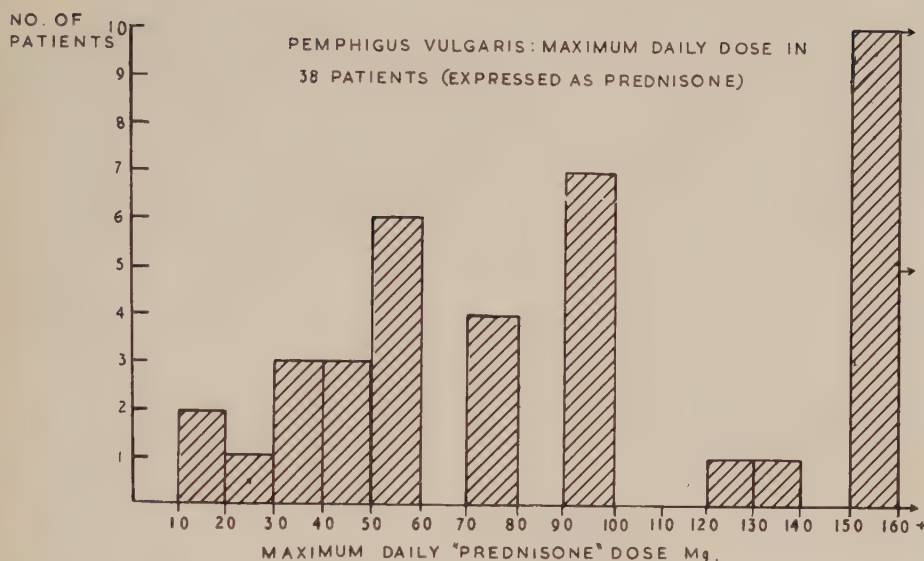


FIG. 2.

Complications.

Complications in surviving patients included pneumonia, haematemesis, thrombotic episodes, skin sepsis, mental symptoms, cardiac failure and osteoporosis. They will be discussed together with those of pemphigus.

PEMPHIGUS.

Sixty-one patients with pemphigus were treated with corticosteroid drugs. Their average age was 52 years, all but 4 being aged less than 70 years. The overall mortality was 34% in this 7-year study (Table III). This may be

TABLE III.—*Pemphigus Mortality.*

P. vulgaris	.	.	.	39	Mortality	.	.	.	15
P. foliaceus	.	.	.	11	"	.	.	.	2
P. erythematosus	.	.	.	9	"	.	.	.	3
P. vegetans	.	.	.	2	"	.	.	.	1
Totals	.	.	.	61					21 (34%)

(Not given steroids, but followed up—4 patients.)

compared with the series of Costello, Jaimovich and Dannenberg (1957), whose 52 patients suffered an overall mortality of 40% during a 5-year study, and the series of 28 patients of Nelson and Brodey (1955) with a mortality of 25% over a similar period. The mortality in a pre-steroid series of Costello *et al.* (1957) was over 90%.

Causes of Death in Pemphigus.

It is difficult to give a single cause for death in patients when pre-existing disease, the condition under treatment and the side effects of therapy may contribute to varying degrees, but it is instructive to seek the major factor in each case. With this in view, the cause of 21 deaths in this series of 61 patients with pemphigus of all varieties, treated with steroids, is considered under five headings (Table IV) and the case histories are reviewed.

TABLE IV.—*Cause of 21 Deaths in Pemphigus Series.*

	Patients.
(i) Pemphigus—inadequate initial steroid dosage	4
(ii) Pemphigus—maintenance dosage too low—relapse not controlled	4
(iii) Complications under high steroid dosage	6
(iv) Other pathology the main factor	6
(v) Sudden withdrawal of steroid therapy	1

(i) Pemphigus—inadequate steroid dosage.

A man aged 66 died in 1953 within 4 weeks of starting treatment. He had received only 200 mg. of cortisone daily which did not control his pemphigus vulgaris. During the last week of his illness he was given A.C.T.H. but failed to respond, dying with peripheral circulatory failure. Autopsy revealed atheroma of the coronary arteries but the heart appeared normal.

A woman aged 42 died in 1953 within 3 weeks of starting treatment. Her pemphigus vulgaris failed to respond to cortisone, 200 mg. daily.

A man aged 67 was treated in a non-dermatological centre for 3 months before admission to a skin ward. By then he was grossly emaciated and had already been given two short courses of steroids. On admission he failed to respond to prednisone 100 mg. daily and died from pulmonary embolism and pemphigus vulgaris.

A woman aged 64 was admitted initially to a non-dermatological department. Her pemphigus vulgaris was treated with prednisone 20 mg. daily. Over a period of 7 weeks, the dosage was gradually stepped up, various corticosteroids and A.C.T.H. being tried. Her condition was at no time adequately controlled. Finally the patient suddenly became moribund. Autopsy showed a massive adrenal haemorrhage.

Four of the series of Costello *et al.* (1957) and five of that of Nelson and Brodey (1955) were also thought to have died from inadequate steroid dosage. Like the first two patients referred to above, treatment was given in the earlier years of steroid therapy. The last two patients appeared to have developed a resistance to corticosteroids and the importance of a high initial dosage has been reported by many authors. This subject will be discussed further in this paper.

(ii) Pemphigus—maintenance dosage too low—relapse not controlled.

Two patients were victims of circumstance, one dying in relapse in 1952, inadequate supplies of cortisone being available, while the other patient had been taken off steroids 10 days before admission to hospital. She failed to

respond to prednisone: severe anaemia may also have contributed to her death.

Two other patients relapsed following reduction of steroid dosage.

A woman with pemphigus, aged 50, was controlled with the equivalent of 90 mg. of prednisone daily. On reduction to 30 mg. daily, a severe relapse of pemphigus vulgaris occurred which failed to respond to 100 mg. daily, the patient dying from metabolic imbalance, cardiac failure and cardiac infarction.

A man aged 69 had severe pemphigus vulgaris controlled with prednisone for one year. On reduction from an average dose of 35 mg. to one of 25 mg. daily, his pemphigus relapsed, failing to respond to prednisone 200 mg. daily. He died from cardiac infarction.

The latter two patients appeared to show resistance to steroid therapy when in relapse.

(iii) Complications under high maintenance dosage.

Six patients who had been having the equivalent of 200 mg. or more of prednisone died from complications related to therapy. Two had infections (one urinary, one pulmonary) clinically masked by steroids, three had diabetes complicated by lung infection or cardiac failure and one died from right-sided heart failure.

(iv) Other pathology the main factor.

In six patients, death was considered to be due primarily to concurrent disease and not related to pemphigus or to steroid therapy. (Mitral stenosis; pulmonary tuberculosis; cardiac failure at age of 81 years; bronchiectasis and heart failure; cerebral haemorrhage; cardiac infarction during remission from therapy.)

(v) Sudden withdrawal of steroid therapy.

One 51 year old woman who had been having cortisone for 2 years was taken off treatment by a new doctor when she was on holiday. She died with relapse of her pemphigus within two weeks, possibly from suprarenal failure. The importance of this hazard is well recognised.

Dosage of Steroids in Pemphigus.

Fig. 2 shows the maximum dosage in terms of prednisone used in 38 patients with pemphigus vulgaris. In one other patient this information was lacking, treatment having been at several centres. The maximum dose varied from 20 mg. to 400 mg. of prednisone. More than three-quarters of the patients required 60 mg. or more of prednisone. In the other varieties of pemphigus (Fig. 3) half of the patients required 60 mg. or more of prednisone. Reznick *et al.* (1956) recommend prednisone 120 mg. daily in severe cases of pemphigus; Costello *et al.* (1957) advise intravenous corticotrophin in severely ill patients

with painful oral lesions, and prednisone 100 mg. daily in patients with moderately extensive eruptions. The latter figure seems a reasonable guide in the light of experience from the present series. A comparison between the effectiveness of corticotrophin and cortisone analogues has not been attempted here.

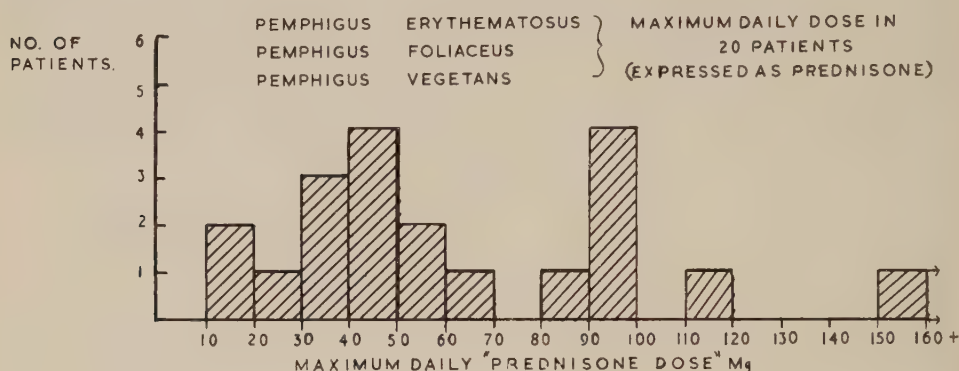


FIG. 3.

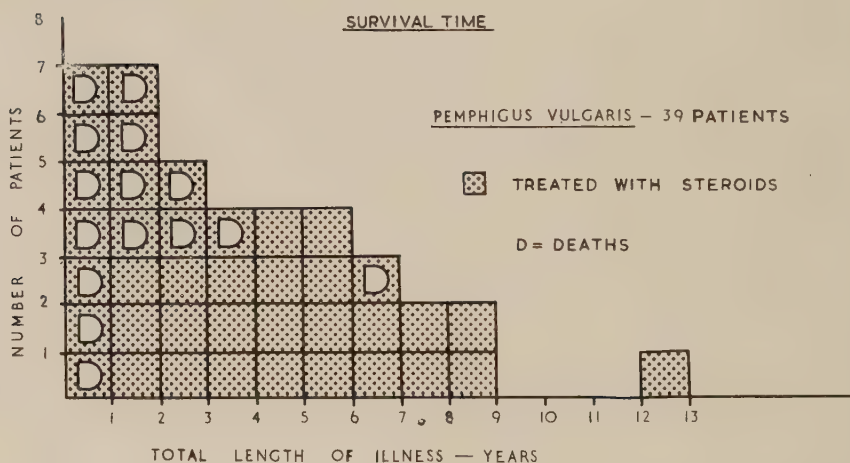


FIG. 4.

Response to treatment.

P. vulgaris.—Of the 39 patients with pemphigus vulgaris, two have remained in remission without treatment for three years, one for two years and one for one year. The total time of survival since the onset of symptoms is shown in Fig. 4. Sixteen patients survived for over four years and one for twelve years.

P. foliaceus.—Corticosteroid drugs were found to be of considerable value in all but two of eleven patients with pemphigus foliaceus. This finding contrasts with that of Costello *et al.* (1957) who found the drugs to be of little permanent benefit. Only three patients in the present series had exfoliation from the entire body surface. One of these responded well to treatment, one derived little benefit, while the third was severely ill and died from intercurrent urinary-tract infection. The remaining patients had large exfoliative areas, biopsy showing acantholysis in the stratum granulosum. One patient has remained symptom free for 6 years since stopping treatment; others had remissions but relapsed. The time of survival since the onset of symptoms is shown in Fig. 5. During this investigation a patient who has never had steroid therapy was found to have survived for seventeen years.

P. erythematosis.—One patient with pemphigus erythematosis failed to respond to steroid therapy. The remaining eight patients responded well, one has been in remission without treatment for eight years. Survival time in this variety of pemphigus is shown in Fig. 5. (In addition, three patients not treated with steroids have survived for eleven, four and two years respectively.)

P. vegetans.—Of the two patients with pemphigus vegetans (Fig. 5) one died mainly from associated bronchiectasis and heart failure.

COMPLICATIONS IN THIS SERIES.

The many reports of the side effects and complications of corticosteroid therapy in the literature include a report concerning 200 patients with skin diseases, by Cronin and Wells (1958). It is therefore only justifiable here to discuss certain features taken from the total series of 172 patients with bullous diseases, although all the common side effects and complications of corticosteroid therapy were encountered.

Pulmonary Tuberculosis.

One patient developed miliary tuberculosis during treatment and this was controlled with chemotherapy. Two patients with pemphigus vulgaris are of interest in this context.

A man aged 31 was found in 1952 to have bilateral pulmonary tuberculosis in addition to pemphigus. He was given local treatment for the skin, also streptomycin and isoniazid. Both skin and pulmonary conditions deteriorated. Two weeks before his death he was given cortisone with temporary benefit.

A man aged 45 was found in 1954 to have a tuberculous cavity in the left upper lobe, as well as pemphigus. He was given vigorous treatment with cortisone and anti-tuberculous therapy, and during remission he underwent lobectomy. He remains well having anti-tuberculous chemotherapy and prednisone.

Angawa and Haynes (1959) have shown that one indication for the use of steroid therapy in tuberculosis is for the desperately ill patient with extensive disease, who may be rescued by such means.

Intercurrent Infection.

Fatal but clinically masked urinary-tract and pulmonary infections have been referred to earlier in addition to two instances of lung abscess. Such

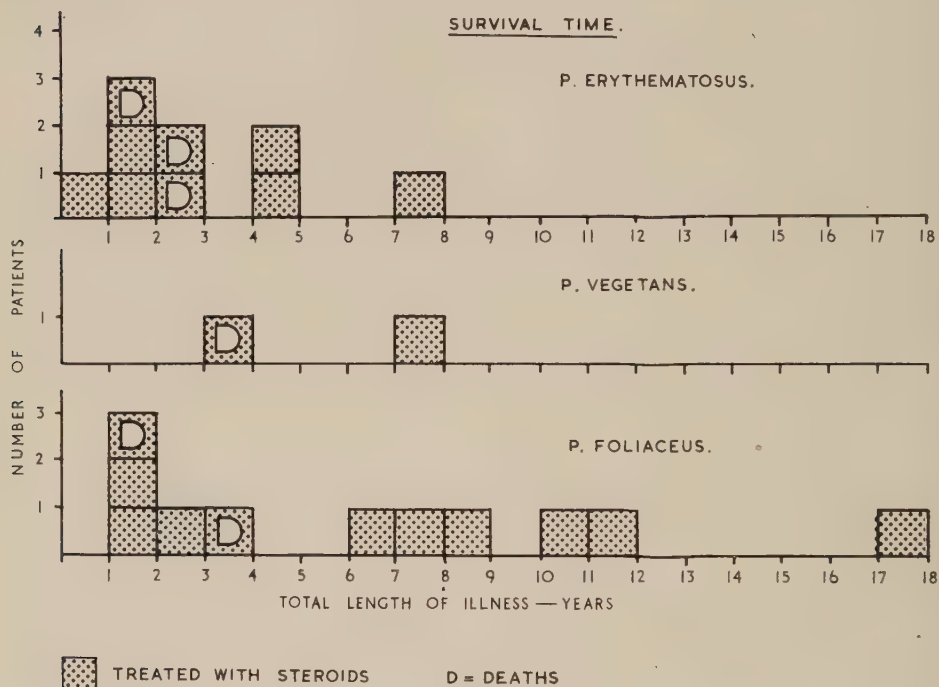


FIG. 5.

episodes are amongst the most dangerous hazards of steroid therapy. A patient with pemphigus vulgaris from this series, who, having survived partial gastrectomy earlier in her illness, developed gangrene and osteomyelitis of her hand, was reported by Russell (1959).

Cardiac Infarction.

One patient with cardiac infarction had severe diabetes and a lipaemic state with a blood cholesterol of 1200 mg. per 100 ml. The higher risk of cardiac infarction in patients on corticosteroid therapy who also have a high blood cholesterol has been stressed by Aldersberg *et al.* (1955).

Pregnancy.

It is of interest to record that this natural phenomenon occurred twice in this series of steroid treated patients. In one case the pregnancy was terminated. In the other, pregnancy was diagnosed at 3 months in a patient with pemphigus erythematosus. Steroid therapy was withdrawn and subsequently a child was born but died in infancy with congenital heart disease. During a later remission the same patient became pregnant when not on steroid therapy and gave birth to a healthy child.

SUMMARY.

The results of treatment in 172 patients with various bullous diseases who had corticosteroid hormones or corticotrophin are recorded.

In severe recurrent erythema multiforme, steroids were of value in suppressing attacks especially in Stevens-Johnson syndrome.

Corticosteroids were seldom used in dermatitis herpetiformis (Duhring) and were ineffective in 6 out of the 10 patients treated.

Of 14 patients with benign mucous membrane pemphigoid, 10 were helped by steroid therapy, but suppression of ocular lesions, if present, did not occur. In 4 patients, steroid therapy was ineffective.

Sixty-eight patients with pemphigoid were treated with corticosteroids with good response in all but 6 cases. Two died from complications under steroid therapy.

Sixty-one patients with pemphigus were treated, the overall mortality being 34%. The importance of high dosage of corticosteroids initially and in the treatment of relapses is stressed. Although of greatest value in pemphigus vulgaris, corticosteroids also proved of considerable value in many cases of pemphigus erythematosus and pemphigus foliaceus.

Certain complications occurring in this series are discussed.

I would like to record my thanks to the physicians to the Skin Departments of the following hospitals for their generosity in allowing me access to their case records and for facilities to discuss them:

Charing Cross, King's College, London, Middlesex, Royal Free, St. Bartholomew's, St. George's, St. John's for Diseases of the Skin, St. Mary's, St. Thomas's and University College.

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STEROID THERAPY IN COLLAGEN DISEASES.*

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THE TERM "diffuse collagen disease" was introduced by Klemperer and his associates (1942). In applying the term to systemic lupus erythematosus and systemic scleroderma, they wished to emphasise that the principal pathological change observed in these diseases was a morbid process affecting the entire connective tissue system of the body. The most striking histological change is fibrinoid degeneration, a descriptive term for certain well defined optical and tinctorial alterations in the collagenous fibres and ground substance. Since then the label "collagen disease" has been attached to a great many conditions such as rheumatoid arthritis, acute rheumatism, glomerulo-nephritis, polyarteritis nodosa, temporal arteritis, dermatomyositis, malignant hypertension, thrombo-angiitis obliterans and thrombotic thrombocytopenic purpura, on the basis that in all of these disorders fibrinoid degeneration of connective tissue may be found, particularly in and associated with small blood vessels. This "exaggerated popularity of the diagnosis collagen disease" serves no useful purpose. As Klemperer (1950) says: "There is a danger that it may become a catch-all term for maladies with puzzling clinical and anatomical features. It is not a term applicable to diagnosis and certainly does not define the morbid process of the diseases grouped together. All we wanted to express originally was that in certain diseases anatomical investigations reveal conspicuous alterations of the intermediary substances of the connective tissue in a systemic manner".

It is important therefore that we should be quite clear what we mean by "the collagen diseases" and in this paper I propose to use the term in a restricted sense and to apply it only to those diseases which Talbott (1957) calls the "non-rheumatoid connective tissue disorders" namely, polyarteritis nodosa, systemic lupus erythematosus, progressive systemic sclerosis, dermatomyositis and polymyositis. This restricted interpretation of the term is particularly suitable for our present purpose since all these diseases are of great interest to dermatologists because they frequently present with cutaneous lesions.

The aetiology of these diseases is unknown. There is evidence that hyper-

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sensitivity, probably to drugs and possibly to other noxious agents, is an important mechanism in polyarteritis nodosa (Rose and Spencer, 1957) and this may be true in the other diseases also. It is now believed by many that an alteration in collagen, the intercellular binding substance, is probably not the fundamental change in any or all of them. Whatever their causation they have in common the fact that they all show a symptomatic response, often only temporary, to treatment with either the adrenal steroid hormones or corticotrophin and this is the subject of my paper. Although all these conditions appear to be occurring more frequently in recent years, they are still relatively rare diseases and it is difficult for one physician, even if he is particularly interested in this field, to acquire sufficient experience of any one of them, let alone the whole group, to enable him to express any strong personal opinions about their treatment. I propose, therefore, first of all to discuss the effects of treatment in the individual diseases, drawing both upon the information in the literature and my own rather limited experience and then to consider some of the problems of steroid therapy in these diseases.

POLYARTERITIS NODOSA.

I begin with polyarteritis nodosa because of the four diseases it is the one in which we have the best evidence of the effects of steroid therapy. Early reports (Rose, Pare, Pump and Stanford, 1950; Shick, Baggenstoss, Fuller and Polley, 1950; Symmers and Litchfield, 1952), indicated that both corticotrophin and cortisone could produce a good symptomatic response in some cases but that relapses usually occurred when the drugs were stopped. As the drugs became more readily available and the newer compounds with fewer undesirable side effects came into use, larger doses and more prolonged courses of treatment have been given and the results have been more favourable (Steinberg and Roodenburg, 1956; Gregoire and Rose, 1957). I think that most people would now agree that steroid therapy is the treatment of choice in polyarteritis nodosa.

In this country the Medical Research Council (1957) has published a report in which the survival rates of 17 patients treated with cortisone were compared with those of 19 patients not so treated. All the cases were proved by biopsy but the non-treated cases were a retrospective series. The results of this trial are subject to the fallacies of using a retrospective control series and partly for this reason they are not as conclusive as one would wish. They do, however, suggest that in addition to producing a symptomatic remission, cortisone does in fact prolong life in patients with this disease.

Complete suppression of symptoms is difficult to achieve and may require an initial high dosage, 300–500 mg. of cortisone daily or its equivalent as prednisone or one of the other analogues, followed by prolonged maintenance

therapy. There has been a report of at least one case (Dent, Strange, Sako and York, 1953) in which an apparent cure was achieved ; the drugs were stopped after 55 days and the patient remained well thereafter. Such a case is exceptional and my own experience and the results reported in the literature suggest that in the majority of cases treatment must be continued indefinitely. The specific hazard of treatment in polyarteritis nodosa is that rapid healing of the characteristic vascular lesions may be accompanied by arterial occlusion which results in visceral infarctions and if these occur in vital organs they may prove fatal (Baggenstoss, Shick, and Polley, 1951 ; Drury, Hickey and Malone, 1951 ; Hench, 1956). Patients who are being treated for rheumatoid arthritis with cortisone or one of the allied drugs may rarely develop the features of polyarteritis nodosa while on steroid therapy. In such cases the correct treatment is not an increase in the dose of steroids but a very gradual reduction in the amount of the hormones (Slocumb, Polley and Ward, 1957).

SYSTEMIC LUPUS ERYTHEMATOSUS.

The situation is rather different in systemic lupus erythematosus. Here we are dealing with a disease which has all gradations from the relatively benign skin condition of chronic discoid lupus erythematosus or a mild rheumatoid type of arthritis to an illness with severe constitutional disturbance and extensive visceral lesions which may rapidly prove fatal. Moreover there are other drugs, notably salicylates and the anti-malarial preparations mepacrine, chloroquine, hydroxychloroquine (Plaquenil) and amodiaquine (Camoquin), which may induce remission in at least some of the clinical features. Thus, although there are those who believe that "every patient with systemic symptoms in whom a diagnosis has been suspected or has been confirmed should receive adequate amounts of steroids" unless there are definite contraindications (Talbot and Ferrandis, 1956), the majority believe that this form of treatment should be reserved for the acutely ill patient and for those who are disabled and have not responded to other forms of treatment. In America, Dubois (1956*a* and *b*) who has the greatest experience in this field, certainly adheres to this view and in this country Hill (1957) has said, "while it is unwise to temporise with less potent measures in an extremely ill patient the automatic use of hormones in milder cases is to be sternly discouraged". If steroid therapy is to be used the drugs must be given in a dosage sufficient to suppress the clinical features. Dubois has used doses as high as 4000 mg. of cortisone a day or 160 mg. of prednisone a day for as long as a month. I have not personally had to give doses of this magnitude but I would agree that in most cases the majority of the clinical manifestations can be suppressed by adequate treatment and that in many instances failure to respond is due to insufficient dosage. The one clinical feature which does not respond to steroid therapy is renal

failure. Once this is established the prognosis is poor. Dubois (1956b) has reported that some improvement in renal function may follow treatment with nitrogen mustard, but I have no experience of this. When the clinical features are under control, the erythrocyte sedimentation rate normal and the anaemia corrected, the dose of the drug may be reduced gradually. The possibility of inducing a permanent remission so that the drug may be withdrawn completely is said to be greater in systemic lupus erythematosus than in polyarteritis nodosa. Dubois (1956b) reports that this happened in 37% of his cases, but my own experience has been that all patients require some steroid therapy to keep them symptom free. The maintenance dose may, however, be as low as 10 mg. of prednisone daily. The combination of hydroxy-chloroquine or one of the other anti-malarial drugs with an adrenal steroid such as prednisone is now being advocated as a means of keeping the dose of the latter at a reasonable level. Clinical remission may be accompanied by a disappearance of the L.E. cell phenomenon from the blood but this is not always the case (Talbot, 1957).

PROGRESSIVE SYSTEMIC SCLEROSIS.

By progressive systemic sclerosis I refer to that form of "scleroderma" which begins with attacks of the Raynaud phenomenon in the fingers, is followed by sclerotic changes in the skin of the extremities (acrosclerosis) and is frequently accompanied by arthritis, polymyositis and visceral lesions especially in the oesophagus and lungs. Although I am one of those who believe that there is no clear division between this disease and dermatomyositis I propose to deal with the two conditions separately.

Opinions vary about the value and about the advisability of using steroid therapy in progressive systemic sclerosis. Early reports (Bayles, Stout, Stillman and Lever, 1950; Kierland and Hines, 1951) indicated that short courses of either corticotrophin or cortisone could produce relief of pain, stiffness and swelling when this was present and might also cause a feeling of general well-being with gain in weight. When the drugs were stopped relapse invariably followed, within a few days as a rule, although one of the cases reported by Kierland and Hines (1951) had a remission lasting for five months. Taubenhaus and Lev (1951) reported one case in which they claimed that serial skin biopsies during and after treatment showed improvement in the histological changes. Attempts to maintain the initial improvement by continuing maintenance therapy have not been as successful as in either polyarteritis nodosa or systemic lupus erythematosus and there have been reports of serious and fatal aggravations of the disease following long-term therapy. The main complication has been a syndrome of malignant hypertension reported by Lunseth, Baker and Shifrin (1951), Sharnoff, Carideo and Stein (1951), and Bartels, Christensen

and Ohlsen (1955). It is to be noted, however, that this syndrome is well known as a terminal event in untreated progressive systemic sclerosis. O'Leary and Erickson (1953) state that they now regard atherosclerosis as a definite contraindication to the use of cortisone or corticotrophin and that they know of six cases in which young women with atherosclerosis died of cerebrovascular accidents associated with severe hypertension.

Zion, Goldberg and Suzman (1955) treated 14 patients with either cortisone or corticotrophin. Four had moderate to marked improvement and nine had slight improvement. They state that in one patient there was clinical and histological reversal to normal. They believe that patients who have a history of less than six months and who have no peripheral vascular disturbances show the best response. When treatment was stopped the improvement was not maintained and in most of their cases they were continuing with the drugs. Salomon, Appel, Dougherty, Herschfus and Segal (1955) reported the effects of a five week course of cortisone on the pulmonary function and skin histology of three patients. They state that in spite of subjective and apparent objective improvement in all the patients, there was no change in the results of the tests of pulmonary function or in the skin biopsies and that relapse occurred when therapy was stopped. Rodnan, Black, Bollet and Bunim (1956) used prednisone and reported favourably on the degree of symptomatic improvement particularly as regards skin changes and arthritis but they also did not observe any alteration in the histology of the skin. They comment that patients with oesophageal involvement did not obtain any improvement in their dysphagia but one patient with pulmonary changes experienced marked improvement in dyspnoea.

I have a greater personal experience of this disease than with any of the other conditions considered here. Except in cases with a minimal degree of atherosclerosis I have invariably prescribed steroid therapy since cortisone and its analogues became freely available. I have never seen any serious untoward effects on the disease following the use of these substances either when given in short intermittent courses, as I did at first, or following their long-term use which is now my policy. I know of no other form of treatment which can produce such a beneficial effect in this disease. The results are never dramatic but I am convinced that steroid therapy helps both the cutaneous and arthritic features and improves muscle power when there is some degree of polymyositis. I am less certain about the effect upon the visceral manifestations; dysphagia does not improve, but like Rodnan and his colleagues I have one patient with pulmonary changes who has experienced considerable improvement in her breathlessness. I usually start the patient on a daily dose of 40 mg. of prednisone or its equivalent and once the clinical improvement is obvious, I reduce the dose gradually to a maintenance level of 10–15 mg. of prednisone daily. I now have several patients who have been on this dose for more than two years.

DERMATOMYOSITIS AND POLYMYOSITIS.

Dermatomyositis may be defined as an acute, subacute or chronic disease of unknown origin characterised by oedema, dermatitis and multiple non-suppurative inflammatory lesions in muscle. Physicians, if not dermatologists, have recognised for some time that similar cases can occur without skin lesions and that when such cases run a subacute or chronic course the clinical picture may closely resemble that of a muscular dystrophy. For the whole group of cases the term polymyositis is most appropriate.

The acute form of dermatomyositis was one of the conditions in which it was early shown that remission could be induced by treatment with either corticotrophin or cortisone (Elkinton *et al.*, 1949; Oppel, Coker and Milhorat, 1950; Thorn *et al.*, 1950). Subsequent reports both from America (Domzalski and Morgan, 1955) and in this country (Suzman and Rudolph, 1951; Clein, 1953; McElligott, 1956) have confirmed this. Although dramatic symptomatic improvement may occur in some of these acute cases this is not always followed by a prolonged remission and even if therapy is continued, the end result of treatment is often disappointing (Wedgwood, Cook and Cohen, 1953; Smith, 1955; McElligott, 1956). In the subacute or chronic forms of the disease the results are variable, some patients respond well and others only slightly or not at all (Walton and Adams, 1958). In spite of the unpredictable nature of the results of steroid therapy there is no other form of treatment which may influence the course of the disease so dramatically and as in polyarteritis nodosa, I think there would be general agreement that steroid therapy is the treatment of choice in dermatomyositis. The largest reported series that I have found is that of Christianson, Brunsting and Perry (1956). They treated 62 patients; 28 were improved and 9 obtained a complete remission. Twenty-six of their patients were treated for less than three months and thirty-six for a period ranging from three months to five years. As is well known dermatomyositis may be associated with malignant disease. Even in such cases the dermatomyositis may respond to treatment with cortisone (Simpson, 1953; Walton and Adams, 1958).

My own experience with dermatomyositis is confined to a single patient whom I have now treated continuously with steroids for more than five years. She had a typical acute illness at the onset which responded to intermittent courses of cortisone and corticotrophin. After a period of remission she relapsed and has since required relatively large doses of steroids (200 mg. of cortisone daily or its equivalent) to keep her moderately well. Any attempt to reduce the dose or to withdraw the drug is followed by a flare-up of her symptoms, so that even now treatment is apparently effective only in the sense that the disease is being suppressed.

In dermatomyositis the dosage of steroids does not apparently need to be very large. A maximum initial dose of 300 mg. of cortisone daily or its equivalent is usually sufficient in an adult to induce a clinical remission and in most of the reported cases the maintenance dose has been lower (50–75 mg. daily) than that which I have found necessary in my patient. The duration of treatment may be anything from six weeks to an indefinite period which may be at least five years.

PROBLEMS OF TREATMENT.

Choice of Drug.—Both corticotrophin and all the available adrenal steroids are effective in inducing remissions in these so-called “collagen” diseases and there is little evidence that any one of them is more effective than the others. Choice of drug depends therefore on factors other than their therapeutic effectiveness. Since treatment nearly always has to be continued for a considerable time there seems to be no good reason to use a preparation which has to be given by injection and except in a very acutely ill patient there is no real advantage to be gained by using corticotrophin. As regards the adrenal steroids the fact that the newer preparations triamcinolone and dexamethasone are effective in lower dosage makes little difference; if a patient has to take four tablets daily it does not matter to him whether these are 25 mg. tablets of cortisone or 1 mg. tablets of dexamethasone. Since all are effective therapeutically the best drug is undoubtedly that which produces the least in the way of side effects. None unfortunately is free from this drawback. Triamcinolone has apparently the specific disadvantage that it may produce profound muscle weakness (Williams, 1959) and this makes it an undesirable drug to use in diseases which may themselves be associated with damage to muscle. Prednisone and prednisolone have the advantage over cortisone and hydrocortisone that they are less liable to cause electrolyte disturbances and I regard them as the best drugs at present available for the treatment of these diseases. Personally I do not think that there is any difference between the therapeutic effectiveness of these two substances but Dubois (1956a) states that he has found prednisone the more effective in the treatment of systemic lupus erythematosus.

Hazards of treatment.—Since one often has to use large doses initially and continue treatment for long periods, steroid therapy of the collagen diseases is beset with all the hazards that may befall patients who have to take these drugs. The development of a “moon face” and a mild degree of acne are almost inevitable effects of long-term therapy and probably must be accepted, but the more serious side effects such as hypertension, electrolyte disturbances, osteoporosis, peptic ulceration and its complications, diabetes and sudden death from adrenal failure have all been reported.

Personally I have been fortunate. Nearly all my patients who are on long-term treatment have complained of purpura and subcutaneous bruising especially in the lower limbs. One of my patients with polyarteritis nodosa died suddenly with a mild respiratory infection. This was almost certainly due to adrenal failure and I have the impression that this may be a greater hazard in those who are on small doses of steroids. They are given sufficient hormone to suppress their endogenous adrenal secretion but do not have enough to tide them over an emergency. This might be an indication to give such patients a weekly booster dose of corticotrophin gel as is advocated by some people but I have not yet done this routinely. My patient with dermatomyositis who has been on relatively large doses of cortisone has radiological changes of osteoporosis and has sustained spontaneous rib fractures. She also has a mild degree of hypertension. Peptic ulceration is said to be the great bug-bear of steroid therapy but none of my patients has been troubled with this although I do not prescribe an ulcer diet, antacids or cholinergic drugs. Nor has steroid-induced diabetes been a problem in this group of cases although I am certain from recent experience in other cases that it is a major hazard of treatment with prednisone and one which may apparently develop rapidly without the warning of a symptomless glycosuria.

CONCLUSION.

The advent of steroid therapy has undoubtedly led to a remarkable change in the clinical picture of these rare collagen diseases. In the acute fulminating forms, remissions, previously uncommon, are now often seen. In the subacute and chronic forms the results of treatment are less dramatic, but frequently a worthwhile improvement is obtained. The best results are seen in systemic lupus erythematosus; in polyarteritis nodosa and dermatomyositis the results are not quite so good and in progressive systemic sclerosis the most one can hope for is slight improvement. In any of these diseases the patient is seldom cured and in the majority of cases long-term treatment for an indefinite period is necessary. The patient may therefore be subject to any of the side-effects of steroid therapy. Some of these are not serious and they are a small price to pay for suppression of a disease which might be fatal or at best crippling, but others are serious and even potentially fatal. These are the facts which must be considered when any decision to start a patient on steroid therapy is made.

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ADRENAL CORTICAL FUNCTION AFTER STEROID THERAPY.*

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ELECTROLYTE changes and other toxic results of corticosteroid therapy are well known and the search continues with some success for new cortisone-like substances which will have fewer undesirable side effects. Nevertheless, one major and serious result of such therapy is likely to remain, for if drugs with an adrenal cortical hormone-like action are supplied to the body exogenously, then physiological production by the adrenal cortex may be expected to diminish or to cease altogether. The newer synthetic derivatives of cortisone, since they are reputed to cause no electrolyte or other major disturbances, possibly have the disadvantage that their use may be accompanied by a false sense of security. When patients are given prolonged corticosteroid treatment, suppression and atrophy of the adrenal cortex may be produced and this may result in severe shock or death when surgical procedures are carried out. Such adrenal suppression may continue for periods of up to two years after treatment has been discontinued and during this time the patient is at risk when even minor dental operations are carried out. In this connection many reports have appeared in the world literature and in this country Bayliss (1958) has drawn attention to the problem. This grave danger is one of the major considerations in prolonged steroid therapy and it is becoming ever more necessary to have some satisfactory method for investigating the responsiveness of the adrenal cortex. Estimation of urinary 17-ketosteroids gives a rather poor indication of adrenal cortical function since for the most part they are metabolites of adrenal androgens which are among the least important of the adrenal steroids. In the male, approximately one third represent metabolites of testosterone and in the female possibly small amounts arise from precursors which have been secreted by the ovaries. In both sexes, the remaining 17-ketosteroids are thought to be derived from steroids which have been elaborated by the reticular zone of the adrenal cortex and they may be greatly reduced in any serious illness, while glucocorticoid production, which is thought

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to take place in the fascicular zone of the adrenal cortex, may at the same time remain unchanged. Of the glucocorticoids in peripheral blood, hydrocortisone and corticosterone are the two main adrenocortical hormones, but hydrocortisone is secreted in much larger quantities than corticosterone. Several quantitative methods have been devised to measure the 17-hydroxycorticosteroids (17-OHCS), which comprise hydrocortisone and its metabolites, in blood and urine. Unfortunately although much work has been done, the complexities of adrenal physiology and the difficulties of present techniques present great problems. Few publications on this subject have appeared in this country and it is difficult to be certain even of normal values for plasma and urine, since published figures are based on very small numbers. Nevertheless, it was considered that it might be worth while to make some attempt to assess the state of responsiveness of the adrenal cortex in patients who had previously received corticosteroid treatment.

INVESTIGATION.

In the recent investigation, plasma and urine estimations of 17-OHCS were carried out in a number of patients before and after maximal stimulation of the adrenal cortex by adrenocorticotrophic hormone. Patients who were suffering from Besnier's eczema and who had received corticosteroids for four or more months were selected. Further selection occurred because a few refused to co-operate. Thirteen patients including four control cases of Besnier's eczema were investigated by the method of intravenous stimulation with A.C.T.H., and five children including one control were investigated by intramuscular injection with A.C.T.H. gel. The study, which has been in the nature of a "pilot" investigation, was limited by clinical and technical difficulties and it was not practicable to carry out observations for more than 48 hours in each case. Accordingly, one 24-hour collection of urine was taken for estimation of the total 17-OHCS as a basal reading, then at 9 a.m., approximately 90 mg. of A.C.T.H. were given by intravenous drip in 1 pint of normal saline over four hours. Approximately 25 ml. of peripheral venous blood were withdrawn immediately before the infusion was started and similar blood specimens were taken off at 2 hours and at 4 hours for plasma estimations. A second 24-hour collection of urine was made from the time the drip was started. In children an intramuscular test of 40 mg. A.C.T.H. gel. was given and urine studies only were carried out.

A modification of the method of Nelson and Samuels (1952) was used to measure the plasma 17-OHCS (more correctly referred to as the Porter Silber chromogens). The total urinary 17-OHCS were measured by the method of Appleby and his colleagues (1955) modified by Nabarro and his co-workers (1957). These methods for plasma and urine estimations are generally accepted as giving reasonably reliable values for hydroxycorticoids. Total urinary 17-OHCS include a wider range of metabolites than the Porter Silber reaction used in plasma estimations and therefore a strict parallelism between plasma and urine results is not to be expected.

RESULTS.

The first three tables show details of the cases in order of investigation. Controls were introduced unknown to those carrying out the biochemical tests. With regard to preceding steroid therapy, no case received a so-called

"loading dose" at the commencement of treatment and maintenance doses except in three cases ranged from 5 to 15 mg. of prednisolone daily.

Table I.—The detail in each case is listed vertically below the case number. Against duration of therapy, the steroid given is represented by an initial, followed by the number of months on treatment. Interrupted treatment is indicated by a dash. Stars are placed where there may be some doubt regarding urine findings when volume and creatinine content are considered. We are mainly concerned with the urine and plasma 17-hydroxycorticosteroid responses to the intravenous injection of A.C.T.H. and these responses are listed in the two lowest groups under urine and plasma 17-OHCS.

TABLE I.—*Adrenal Cortex Stimulation Test. A.C.T.H. 90 mg. i.v. over 4 Hours.*

Case No.	1.	2.	3.	4.	5.	6.	7.
Age and sex	38 M.	24 F.	26 M.	20 M.	19 M.	17 M.	29 M.
Duration of steroid therapy (months)	P. 3— A. 13 P. 8	P. 23	P. 7— P. 5½	P. 2— P. 12	Nil	P. 23 A. 19	P. 6
Off treatment (months)	9½	3	9½	½	—	2½	10
24-hr. urine vol. (ml.)—							
Before A.C.T.H.	1870	1660	920	1790	1050	700	1750
After A.C.T.H.	1490	1470	1080	1400	1020	380	1100
Urine creatinine (g./24 hr.)		*			*	*	*
Before A.C.T.H.	1.68	1.43	1.47	1.54	1.6	0.64	1.85
After A.C.T.H.	1.6	1.15	1.36	1.57	1.2	0.32	1.52
Urine 17-OHCS (mg./24 hr.)							
Before A.C.T.H.	17.5	25.1	16.2	31.4	19.7	—	13.1
After A.C.T.H.	18.6	27.1	26.4	30.8	20.8	5.5	16.5
Plasma 17-OHCS (μg.%)							
Before A.C.T.H.	0	0	0	21	21	8	13
After A.C.T.H. 2 hr.	0	0	0	21	30	33	23
After A.C.T.H. 4 hr.	10	0	5	24	36	24	26

P. = Prednisolone.

A. = A.C.T.H.

(Case I received prednisolone for a total of eleven months concurrently with A.C.T.H. gel. 10 mg. twice weekly for thirteen months. All treatment had been discontinued for 9½ months at the time of investigation. Urine total 17-OHCS were within the normal range which Nabarro and his colleagues (1957) found to be from 7.3 to 23.6 mg./24 hours in males. However, a satisfactory increase did not take place after the stimulation test which in the normal subject may be expected to produce at least a twofold increase. Plasma values were significantly low and showed only a small, delayed response to A.C.T.H. In normal subjects, Bayliss and Steinbeck (1954) found a mean value of 9.5 μg. 17-OHCS per 100 ml. plasma with limits of 3–16 μg. in 95% of cases. They found that maximal stimulation by intravenous A.C.T.H. raised the range into the level of 24–36 μg. per 100 ml. In normal subjects then, an increase of at least 15 μg. per 100 ml. may be expected after intravenous stimulation with A.C.T.H. Furthermore, such maximal stimulation will produce a slight

rise in plasma 17-OHCS within 15 to 30 minutes and a definite increase in one hour. Thereafter during the period of infusion the values remain relatively constant. The first case would therefore appear to be one in which some adrenal cortical suppression was still present 9½ months after steroid therapy had been discontinued. Against this, it may be argued that a normal basal level of urinary corticoids was present, but it has been found by Eik-Nes and his co-workers (1955), Haydar and his colleagues (1958) and by others that partial adrenal cortical insufficiency may exist. In such cases normal basal levels of 17-OHCS are found in urine, but no rise of steroid excretion takes place on administration of A.C.T.H. It may be postulated in these cases that the remaining cortical cells are secreting at their maximum capacity to maintain homeostasis and therefore additional exogenous A.C.T.H. fails to stimulate further production of cortical hormones.

Case 2 received prednisolone for 23 months and treatment had ceased for 3 months at the time of investigation. A high resting level of urinary corticoids was found, the normal values varying from 4.6 to 17.8 mg./24 hours in females. No satisfactory increase occurred on administration of A.C.T.H. while the plasma showed a complete lack of response. It may be significant that this case, which appears to show persisting adrenal cortical suppression, at one period over a few weeks received 25 mg. prednisolone daily, which was the highest dose given in this series.

Case 3, treated with prednisolone for 12½ months, had been off treatment for 9½ months when the test was carried out. Urine results indicated a moderate response to stimulation, but the plasma increase was delayed and inadequate.

Case 4 received prednisolone for a total of 14 months and treatment had been discontinued for 1 week at the time of investigation. High values for hydroxycorticoids were found in urine and plasma but the response to stimulation in both was inadequate.

Case 5, a control case of untreated Besnier's eczema, showed a normal plasma response but urine results were unsatisfactory.

Case 6 received prednisolone for 23 months. During the latter part of this period and for a few weeks thereafter A.C.T.H. gel 10 mg. twice weekly was also given. Two and a half months after this treatment was discontinued, plasma hydroxycorticoid response to the stimulation test was good. Urine collections were unsatisfactory.

Case 7 received prednisolone for 6 months and this had been discontinued for 10 months when the test was carried out. No significant increase in urine hydroxycorticoids took place, but the plasma response was satisfactory.

Table II.—The data are presented as in Table I. Cases 8, 9 and 12 were control cases of untreated Besnier's eczema. Urinary corticoid responses to the test appeared to be normal in only two of these controls (8 and 9), but all three plasma results showed a satisfactory normal increase.

TABLE II.—*Adrenal Cortex Stimulation Test. A.C.T.H. 90 mg. i.v. over 4 Hours.*

Case No.	8.	9.	10.	11.	12.	13.
Age and sex	14 M.	46 F.	61 M.	19 M.	25 M.	21 M.
Duration of steroid therapy (months)	Nil	Nil	A. 6 P. 33	P. 9 T. 3 M. 3½	Nil	M. 5
Off treatment (months)	—	—	0	0	—	0
24-hr. urine vol. (ml.)						
Before A.C.T.H.	1680	1420	2030	1280	1080	1640
After A.C.T.H.	2360	1590	1050	1480	1100	2040
Urine creatinine (g./24 hr.)	*	*	*	*	*	*
Before A.C.T.H.	0.77	0.88	1.22	1.36	1.27	1.31
After A.C.T.H.	1.4	0.8	1.03	1.57	1.23	1.63
Urine 17-OHCS (mg./24 hr.)						
Before A.C.T.H.	21.8	16.1	19.3	23.3	13.2	15.4
After A.C.T.H.	37.8	27.6	24.0	32.6	15.4	32.2
Plasma 17-OHCS (µg.%)						
Before A.C.T.H.	15	12	13	4	13	18
After A.C.T.H. (2 hr.)	27	32	17	25	27	23
After A.C.T.H. (4 hr.)	29	36	22	24	34	24

P. = Prednisolone.

T. = Triamcinolone.

M. = Methylprednisolone.

A. = A.C.T.H.

Cases 10, 11 and 13 were still on maintenance therapy at the time of investigation. Although urine values showed a rise after stimulation by A.C.T.H., creatinine values were rather unsatisfactory thus rendering the interpretation doubtful. With regard to plasma values, cases 10 and 13 showed increases which however were smaller than the normal. Case 11 gave a good normal response.

Table III.—This shows urinary corticoid responses in 5 children who were tested by intramuscular injection of 40 mg. of A.C.T.H. gel. In children, normal basal levels of urinary hydroxycorticoids are probably below 10 mg. per 24 hours.

TABLE III.—*Adrenal Cortex Stimulation Test A.C.T.H. 40 mg. i.m.*

Case No.	1.	2.	3.	4.	5.
Age and sex	5½ M.	5 M.	10 F.	9 M.	11 M.
Duration of steroid therapy (months)	P. 9- P. 1	Nil	— P. 12	— P. 10	P. 12 T. 18
Off treatment (months)	14½	—	8	26	0
24-hr. urine vol. (ml.)					
Before A.C.T.H.	900	250	500	700	990
After A.C.T.H.	910	104	440	460	820
Urine creatinine (g./24 hr.)					
Before A.C.T.H.	0.68	0.23	0.26	0.63	0.61
After A.C.T.H.	0.67	0.05	0.42	0.38	0.51
Urine 17-OHCS (mg./24 hr.)					
Before A.C.T.H.	6.8	2.1	3.8	9.1	7.4
After A.C.T.H.	10.2	3.7	11.4	9.2	10.7

P. = Prednisolone.

T. = Triamcinolone.

Case 1 received prednisolone for a total of 10 months and was off treatment for $14\frac{1}{2}$ months at the time of investigation. A moderate response to the stimulation test was obtained.

In Case 2, a control, the results were invalid because of unsatisfactory urine collection.

Case 3 received prednisolone for 12 months: 8 months after treatment the stimulation test gave a normal response although urine volumes and creatinine were unsatisfactory.

In Case 4, the apparent absence of response is discounted by unsatisfactory urine volumes.

Case 5 which was still being maintained on small doses of triamcinolone showed a slight response to A.C.T.H. stimulation.

DISCUSSION.

A histogram of the urine findings (Fig. 1) in all 13 subjects of the intravenous A.C.T.H. test showed clearly that, at least in the present small series, this method of assessing adrenal cortical function has been unsatisfactory, for only two of the four controls showed a response to stimulation. The figures at the

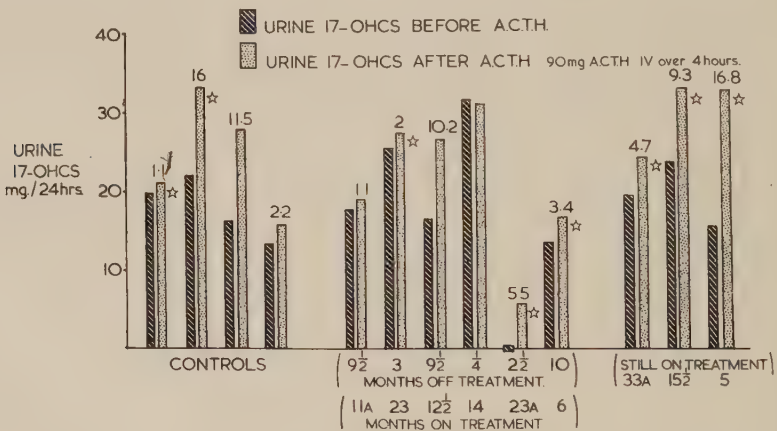


FIG. 1.

top of the columns give the total 17-OHCS increase in mg./24 hrs. after A.C.T.H. stimulation. The normal increase should be at least double the resting level. When the six cases which had been off treatment for periods varying from one week to ten months are considered, only one showed a moderate response to stimulation (an increase of 10.2 mg.) and indeed the three cases which were still on treatment showed increases which more resembled the control group. One can but reflect that in a busy general ward, even with intelligent patients

who are greatly interested in an investigation, the difficulties of urine collection are such as to render findings of very doubtful significance.

A histogram of the plasma results (Fig. 2) is perhaps of greater interest and significance. The four controls show a good normal response to the A.C.T.H. stimulation test with increases of plasma 17-OHCS varying from 14 to 24 $\mu\text{g.}\%$. This corresponds well with the expected normal response of an increase of 15 $\mu\text{g.}\%$ or more after intravenous A.C.T.H.

When the six cases which had been off treatment for varying periods are considered, results suggest that some degree of adreno-cortical insufficiency was present in four of them. In these four subjects, the maximum increases

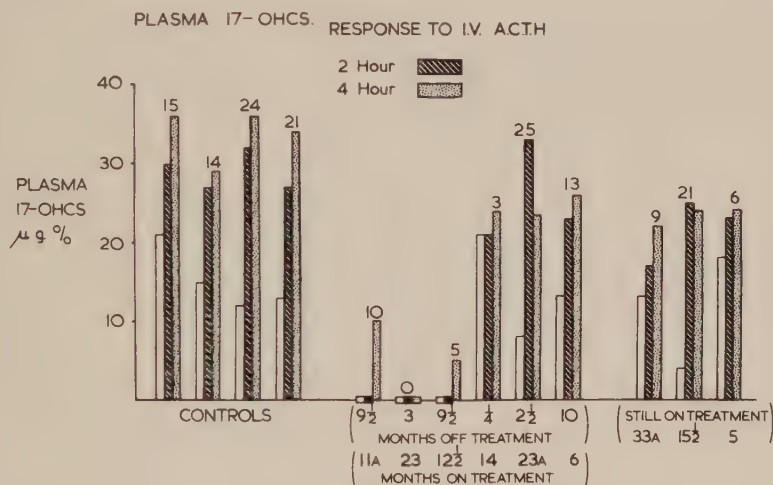


FIG. 2.

in plasma hydroxycorticoids varied from 0 to 10 $\mu\text{g.}\%$ and the responses were greatly delayed. The remaining two cases in this group showed satisfactory increases.

Of the three cases still on treatment, two showed subnormal increases of 6 and 9 $\mu\text{g.}\%$ and one gave a satisfactory increase of 21 $\mu\text{g.}\%$ on stimulation with A.C.T.H.

It is of some interest that three cases received concurrent treatment with A.C.T.H. during maintenance therapy with prednisolone. (These are indicated by an "A" against the number of months on treatment.) Only one showed a satisfactory cortical response (an increase of 25 $\mu\text{g.}\%$) to the stimulation test. This is somewhat in keeping with the findings of Young and his colleagues (1957) who reported that 100 mg. of A.C.T.H. gel weekly failed to maintain normal adrenal responsiveness during corticosteroid treatment and that 200-300 mg. weekly were not always effective. Indeed, on theoretical grounds alone, there would appear to be little justification for the use of A.C.T.H.

as a "booster" during prolonged corticosteroid therapy. Even if it should maintain the function of the adrenal cortex, A.C.T.H. would further inhibit the release of corticotrophin from the pituitary and thus aggravate the interference with the normal pituitary-adrenal responsiveness, for hydrocortisone is a potent inhibitor of A.C.T.H. production. Furthermore, stress, unlike an injection of A.C.T.H., does not act directly on the adrenal cortex, but only at the higher level of cerebral cortex, hypothalamus and pituitary.

CONCLUSIONS.

In the present investigation, the results of urine estimations of total 17-OHCS were of doubtful significance and there was no real correlation between urine and plasma findings. Three day collections of urine, before and after the stimulation test, might have given more valuable results although errors in collection might well have increased. On the other hand, the plasma values obtained in four cases which had been off treatment for periods varying from one week to nine and a half months suggested some degree of adrenocortical deficiency, while the plasma values in two cases, still on maintenance therapy, also suggested diminished responsiveness of the adrenal cortex.

The disturbing results obtained in the plasma investigations must however be considered in relation to certain criticisms. The number of controls is small, the stimulation test might properly be carried out before commencement of treatment as well as during and after treatment and the Nelson and Samules method itself, although the best method available to us, has certain disadvantages for it measures only the "free" forms of plasma corticosteroids. Bongiovanni and his co-workers in 1954 have shown that approximately half of the corticosteroids in plasma are present as conjugates and half are present in the "free" form. The metabolism of adrenal corticoid is very rapid and conjugation takes place quickly. Because of this, although conjugation leads to loss of biological activity, assessment of both "free" and conjugated forms in the blood might perhaps give a more complete picture of the output of the adrenal cortex. In 1955, Weichselbaum and Margraf developed a method for separate determination of free and conjugated adrenocortical steroids in plasma, but the technique is laborious and still subject to methodological change. In any case, Krusius and his colleagues (1958) have found that "free" and conjugated levels in plasma follow each other closely. It may be that in the future, paper chromatographic techniques or procedures employing radioactive steroids will come into general use in the estimation of corticosteroids in blood as well as in urine, for the clinical and therapeutic problems are urgent.

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SIDE EFFECTS OF SYSTEMIC ADRENAL STEROID THERAPY.*

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THE side effects of adrenal steroids are well known in a general way, but it is extremely difficult to obtain a clear idea of which are the most likely to occur, how the different steroids vary in their tendency to produce them, and what is the relationship between dosage and duration of therapy and the side effects observed. There are many reasons for this. One is that so many steroids have become available in a short time. No sooner are figures accumulating about one of them than another is offered to the clinician, launched on such a wave of publicity that it inevitably ousts its predecessors even if its only virtue is a greater apparent efficacy weight for weight. Another reason is that clinicians vary in the care with which they look for side effects, and in the way in which they report those that they do observe. Occasionally one finds in the literature a series of cases of, say, rheumatoid arthritis treated for a year or more with one steroid at a fairly standard dose level in which all the important side effects have been looked for and recorded and their relative incidence established. More often, however, the published data are highly heterogeneous, the patients have been treated for varying times with different steroids in varying dosage and it is impossible to draw clear conclusions. Even more frequently, they deal with individual cases of death or illness due to steroid therapy without reference to the total number of cases treated by the clinician concerned with the particular steroid, and it is then only possible to form the vaguest impression of what is going on. Finally, it is safe to say that only a small proportion of the observed side effects of steroids is ever published, and that the picture one can glean from the literature is at best very imperfect.

The present paper is based on a brief study of the literature on the side effects of steroid therapy, but it has yielded enough information to suggest that the glucocorticoids are probably a great deal more dangerous than most of us realize, and that the main dangers are probably not those which it is fashionable to emphasize at the present time. Thus it was recently suggested that one of the main disadvantages of steroid therapy was osteoporosis (Savage, 1959) but this is an opinion that is scarcely tenable in view of the number of deaths recorded which are directly or indirectly attributable to steroids.

* Based on a paper read at the Thirty-ninth Annual Meeting of the British Association of Dermatology in July 1959.

DEATHS FROM STEROID THERAPY.

I have without difficulty found in the recent literature records of 68 deaths which can probably be attributed to steroid therapy, in series in which the total number of treated cases is shown and some idea can therefore be formed of the mortality on steroid therapy. As in all such studies, it is exceedingly difficult to say in many cases whether a particular death should be attributed to the steroid, but I have only excluded deaths from accident, cancer or other quite irrelevant causes. It will be seen that the mortality in these series varied from 0 to 8% (Table I).

TABLE I.—*Deaths Associated with Steroid Therapy.*

Date.	Authors.	Disease.	Number of cases.	Steroid.	Deaths.
1953	Ziff	Rheumatoid arthritis	446	Cortisone	25 (6%)
1955	Kittredge	Carcinoma of prostate	12	„	1 (8%)
1955	Savage	Rheumatoid arthritis	90	„	6 (7%)
1955	West	Ditto	52	„	2 (4%)
1956	Dubois	Disseminated lupus erythematosus	37	Prednisolone	1 (3%)
1957	Allanby	Miscellaneous	400	Cortisone and A.C.T.H.	14 (4%)
1957	Savage <i>et al.</i>	Rheumatoid arthritis	49	A.C.T.H.	1 (2%)
1958	Cronin and Wells	Skin conditions	200	A.C.T.H., cortisone and prednisolone	6 (3%)
1959	Kendall and Hart	Rheumatoid arthritis	47	Triamcinolone	0 (0%)
1959	Thompson	Ditto	16	Prednisolone and triamcinolone	0 (0%)
1959	Truelove and Witts	Ulcerative colitis	85	Cortisone	7 (8%)

Many of the authors quoted in Table I do not specify the cause of death in the individual cases but simply indicate the total number of fatalities. I have attempted to assess the relative importance of the various causes in 71 deaths associated with steroid therapy as shown in Table II.

TABLE II.—*Causes of Death Associated with Steroid Therapy.*

Cause of death.	Number of cases.	Percentage of total.
Haemorrhage from stomach or bowel	7	10
Perforation of stomach or bowel	13	18
Collapse	10	14
Infection	16	23
Vascular episodes	13	18
Heart failure	7	10
Other causes	5	7
Total	71	

The largest single cause of death in these 71 patients was intercurrent infection which was patent in 16 or 23% (Allanby, 1957; Cohen *et al.*, 1957; Cronin and Wells (1958); Dubois, 1956; Hayes and Kushlan, 1956; Kittridge, 1955; Thompson, 1959 and Ziff, 1953). This was usually bronchopneumonia, but it might be re-activation of pulmonary tuberculosis, septicaemia or bacterial endocarditis.

Another important cause of death is perforation (frequently "silent") of the stomach or small or large bowel (Allanby, 1957; Cronin and Wells, 1958; Hayes and Kushlan, 1956; Kammerer *et al.*, 1958; Fentress, 1956; Pooler, 1958; Sauer *et al.*, 1953 and Truelove and Witts, 1959). which occurred in 13 of these patients (18%). Five of these 13 patients were suffering from ulcerative colitis. Seven deaths (10%) were associated with haemorrhage from the stomach or small intestine (Allanby, 1957; McMahon *et al.*, 1959; Salassa *et al.*, 1953; Savage *et al.*, 1957 and Truelove and Witts, 1959).

Ten patients (14%) collapsed and died after receiving an anaesthetic or after an operation—often a minor one (Cronin and Wells, 1958; Fraser *et al.*, 1952; Kittredge, 1955; Salassa *et al.*, 1953; Slaney and Brooke, 1957 and Truelove and Witts, 1959). Others (not included in Table II) recovered (Harnagel and Kramer, 1955 and Lewis *et al.*, 1953). Some were on steroid therapy at the time of their collapse; in some it had been withdrawn recently or even months before. Some had received ACTH.

Myocardial infarction, cerebrovascular episodes or pulmonary infarction accounted for 13 deaths (18%) (Bunim *et al.*, 1955; Cronin and Wells, 1958; Truelove and Witts, 1959 and Ziff, 1953) and congestive heart failure for 7 (10%) (Allanby, 1957; Cronin and Wells, 1958 and Ziff, 1953). Other specified causes (including diabetic coma) accounted for 5 deaths or 7% (Allanby, 1957; Truelove and Witts, 1959 and Ziff, 1953).

MAJOR NON-FATAL SIDE EFFECTS.

Most of the side effects of steroid therapy are not of course fatal. The total number of side effects attributed or attributable to steroid therapy is very great, but most of them are relatively trivial. Moon face, or "mooning" is an almost invariable accompaniment of effective steroid therapy. In fact, some workers believe that dosage of glucocorticoid is inadequate if a moon face does not develop. Obesity of varying degree, hirsutism, striae, flushing and headaches have all been reported, their incidence probably depending upon the assiduity with which they are looked for.

I will make no attempt to assess the incidence of these minor side effects and will confine myself to the major side effects listed in Table III, which shows only those series in which the total number of treated cases has been reported and in which the complication concerned has been mentioned. Thus

one excellent series of 200 cases (Cronin and Wells, 1958) does not refer to dyspepsia as such, but does report 3 serious gastro-intestinal complications. One cannot conclude from this that none of the other 197 patients had dyspepsia and this series is therefore excluded in considering this particular symptom.

TABLE III.—*Major Non-fatal Side Effects of Steroid Therapy.*

Side effect.	Number affected.	Total in series affected.	Percentage affected.
Dyspepsia	74	385	19
Peptic ulcer	28	630	4½
Hypertension	33	396	8
Osteoporosis	12	437	3½
Diabetes	24	555	4½
Mental disturbances	18	450	4

Dyspepsia and Ulcer.

Dyspepsia is the most prominent and also the least satisfactory side effect to define. There are 385 patients about whom there is some information on this subject (Boland, 1958 and 1959; Fearnley *et al.*, 1957, Kendall and Hart, 1959; Kern *et al.*, 1957; Toone and Irby, 1955) and the incidence is 19% but ranges from 0 to 38%. Certain workers say that its incidence can be reduced by antacids (Boland, 1958 and Dubois, 1956) others that its incidence is related to dosage (Kammerer *et al.*) or to the type of steroid used; it is suggested that prednisolone is more likely to cause it than cortisone (Cronin and Wells, 1958) and that ACTH is less liable to cause it than oral preparations (Morton, 1958). One experienced clinician found 37% of gastric complications on prednisolone, but only 7% on hydrocortisone (Boland, 1956).

Only a small proportion of dyspeptic symptoms associated with steroid therapy is due to proven ulceration of the stomach or duodenum; such ulcers, demonstrated by X-ray or presenting with haemorrhage or perforation, have been recorded in 20 of the 385 patients referred to above (Boland, 1956, 1958 and 1959; Fearnley *et al.*, 1957; Kendall and Hart, 1959; Kern *et al.*, 1957; and Toone and Irby, 1955) and in a further 8 out of 245 (Bunim *et al.*, 1955; Cohen *et al.*, 1957 and Savage *et al.*, 1957) making 28 out of 630 or 4½%. A similar incidence was established by Morton 1958 from a questionnaire survey. Many of those are acute gastric ulcers (Brush *et al.*, 1957) but a number must represent pre-existing duodenal ulcers, and about half the patients are said to give a previous history to suggest this (Sandweiss, 1954). There is some evidence that the incidence is related to the dosage of steroid used (Kern *et al.*, 1957). One clinician found only one ulcer in 49 cases on ACTH compared with 13 out of 83 on oral steroids (Savage *et al.*, 1957). Boland (1959) considers that 9% of patients with rheumatoid arthritis develop peptic ulcer whatever steroid they are on, and advocates routine antacid therapy. Palmer (1959) on the other hand is not convinced of a causal relationship between steroids

and ulcer, but he is in a minority. Healing of peptic ulcers on medical treatment while steroid therapy continues has been reported (Boland, 1959, Fearnley *et al.*, 1957 and Popert and Davis, 1958) and there is one series of 132 cases (Cohen *et al.*, 1957) in which 3 patients with chronic ulcers had no exacerbation.

The pathogenesis of these ulcers is no better understood than that of other peptic ulcers. It is believed that the steroids increase gastric acid secretion (Gray *et al.*, 1956) but steroid ulcers have developed in at least 2 patients with histamine-fast achlorhydria—although it must be stated that the dose of histamine was only 0.5 mg. (Traut, 1958).

Hypertension.

It is undoubtedly true that there is a tendency for the blood-pressure to rise on steroid therapy—particularly on cortisone. But the definition of hypertension is so difficult, and the value of casual blood-pressure readings so controversial, that it is impossible to say what is the incidence of hypertension on steroid therapy. However, taking the various authors' statements at their face value, hypertension has been reported in 33 out of 396 cases, an incidence of 8% (Bunim, *et al.*, 1955; Cohen *et al.*, 1957; Dubois, 1956; Fearnley *et al.*, 1957; Savage *et al.*, 1957; Soffer and Bader, 1952 and Toone and Irby, 1955).

Osteoporosis.

Osteoporosis or fractures have been reported in 12 out of 437 cases or 3½% (Bunim *et al.*, 1955; Cronin and Wells, 1958; Duthie, 1953; Kendall and Hart, 1959; Savage *et al.*, 1957; Soffer and Bader, 1952 and Toone and Irby, 1955) but this must be an under-estimate of the incidence of osteoporosis for at least two reasons. In the first place, there has never been a skeletal X-ray survey of patients before and after a course of steroid therapy. Secondly, osteoporosis has to be moderately severe before it becomes visible on X-rays and a mild degree cannot therefore be excluded by negative X-ray findings. Furthermore, the number of individual case reports (Curtiss *et al.*, 1954; Demartini, 1952; Slaney and Brooke, 1957 and Tiecher and Nelson, 1952) suggests that osteoporosis is not a very rare complication of steroid therapy, although it must be remembered that it is also very common in the population at large.

It is fashionable at the present time to attribute osteoporosis in general and this form of osteoporosis in particular to a disorder of the protein matrix of bone—a failure to form new bone while existing bone is destroyed at the normal rate (Albright and Reifstein, 1948 and Cronin and Wells, 1958). All I wish to say about this hypothesis is that it is not proven, and that it is a little hard to reconcile it with the high faecal calcium which has been observed on steroid therapy (Slater *et al.*, 1959). I am studying the effect of calcium

supplements given together with steroids but it is too early to say whether they have any real effect upon calcium balance.

Diabetes.

It is well known that the glucocorticoids impair glucose tolerance, and glycosuria is not uncommon in patients on steroid therapy. It is far from certain, however, whether the steroids do more than unmask latent diabetes in predisposed individuals, and whether the diabetes produced is irreversible. Diabetes or glycosuria has been reported in 24 out of 555 patients (4%) (Bunim, Ziff and McEwan, 1955; Cohen *et al.*, 1957; Fearnley *et al.*, 1957 and Savage *et al.*, 1957). It has been said that cortisone tends to raise the blood sugar but not to produce ketosis (Kalant, 1958) but this conflicts with at least one published report (Boland, 1958) and with my own experience. I know of two patients who have died in—but not of—ketotic coma.

Mental disturbance.

Mental disturbance, varying from depression or euphoria to frank psychosis, has been reported in 18 patients in 6 series totalling 450 cases (4%) (Cohen *et al.*, 1957; Cronin and Wells, 1958; Israel *et al.*, 1954; Savage *et al.*, 1957; Toone and Irby, 1955 and West, 1955). There is a general feeling that the steroids do not actually cause mental disturbance but uncover or aggravate latent personality disorders.

CONCLUSIONS.

This paper is based only on a rather superficial review of the literature, but the figures given above for the side effects of steroids are probably reasonably representative. It is perfectly clear that there is an appreciable mortality in association with steroid therapy, and that these hormones should be treated with respect. From the point of view of danger both to life and to health, the effects on the gastro-intestinal tract—bleeding or perforation—are clearly among the most important. Intercurrent infection may be lethal in patients on steroid therapy, and so may minor operations not to mention major ones. In a series of 53 operations, shock occurred in 15 of 28 patients who had received steroids and in none of the others (Hayes, 1956). Coronary or cerebral vascular disease accounts for a large number of deaths in these patients, and one wonders if this is connected with the rise in serum cholesterol which accompanies this form of therapy (Bunim *et al.*, 1955). Hypertension does not appear to be a very serious hazard, but diabetes is perhaps more dangerous than is generally believed. Osteoporosis is obviously a very real disadvantage but one can hardly agree that it is one of the main disadvantages of steroid therapy (Savage, 1959) when there are other much more lethal complications.

It is clear that there is an urgent need for careful clinical work on the side effects of steroid therapy. In the meantime one can only conclude that patients should all be provided with a "steroid card" (Duthie, 1958); that they should be warned of the dangers of steroid therapy; that they should be seen frequently and questioned about symptoms; that their urine should be tested regularly for sugar; and that the dose of steroid should be kept as small as possible. Dermatologists are fortunate to be able to use steroids topically and I suggest that they should use them in this way whenever possible.

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CURRENT LITERATURE

SOME HISTOCHEMICAL OBSERVATIONS ON THE HUMAN ECCRINE SWEAT GLANDS.

IV. THE RECOVERY FROM THE EFFECTS OF PROFUSE SWEATING. R. L. DOBSON and W. C. LOBITZ. (1958) *J. invest. Derm.*, **31**, 207.

A histological study of the changes in the sweat gland epithelium during exhaustion in 6 hours of the sweat apparatus by exposure to heat and during a period of recovery. J. H. T. D.

THE EFFECT OF INHIBITION OF NON-SPECIFIC CHOLINESTERASE ON PERCEPTION OF TACTILE SENSATION IN HUMAN VOLAR SKIN. H. J. HURLEY and G. B. KOELLE. (1958) *J. invest. Derm.*, **31**, 243.

Though diisopropylfluorophosphate applied to the tip of the toe produces sweating and can be shown histologically to have inhibited cholinesterase activity around the sensory nerve endings it has no appreciable effect on the perception of light touch pressure and pricking pain. It is already known not to influence itching. J. H. T. D.

EXPERIMENTAL INOCULATION OF HUMANS WITH ECTODERMOTROPIC VIRUSES. H. GOLDSCHMIDT and A. M. KLIGMAN. (1958) *J. invest. Derm.*, **31**, 175.

Unlike vaccinia, warts, molluscum contagiosum, herpes simplex and herpes zoster are inoculated with difficulty. Preparation of the skin by dermabrasion which almost invariably conduces to extra large vaccinia lesions failed to pave the way to successful inoculation of molluscum contagiosum in 30 subjects (total 141 inoculations) of warts in 36 (159 inoculations) herpes simplex 27 (all of whom, it is true, had a C.F. titre of at least 1:8) and of zoster in 23 subjects. Using condyloma acuminatum material, 10 of 47 inoculations were successful; all of them on normal skin, none on the areas prepared either by dermabrasion or cantharides blistering. All this of course contradicts the older literature to some of which reference is made. J. H. T. D.

THE DEMONSTRATION OF ACID SUBSTANCES IN NORMAL SKIN BY ALCIAN BLUE. R. W. GOLTZ, R. M. FUSARO and J. JARVIS. (1958) *J. invest. Derm.*, **31**, 183.

A description of sections of normal skin fixed in formalin stained with Alcian Blue and counterstained with picric acid. Whereas periodic acid Schiff demonstrates all substances containing 1-2 glycol groups, Alcian Blue is specific for acid polysaccharides. J. H. T. D.

REPORT OF A CASE SUGGESTING THE CLINICAL AND MICROSCOPIC PATHOGENESIS OF SARCOIDOSIS. H. E. MICHELSON. (1958) *J. invest. Derm.*, **31**, 171.

The author points out some analogies between the natural history of sarcoidosis and that of miliary tuberculosis. J. H. T. D.

SULPHYDRYL CHANGES IN MOUSE SKIN FOLLOWING AN APPLICATION OF POLYCYCLIC HYDROCARBONS. J. A. Di PAOLO and C. H. U. CHU. (1958) *J. invest. Derm.*, **31**, 167.

The amount of sulphhydryl in the epidermis of mice, as estimated by the inspection of sections stained to show it, appears to be reduced by the previous application of carcinogens. J. H. T. D.

THE WATER CONTENT OF THE STRATUM CORNEUM. IV. THE IMPORTANCE OF WATER IN PROMOTING BACTERIAL MULTIPLICATION ON CORNIFIED EPITHELIUM. I. H. BLANK and RUTH K. DAWES. (1958) *J. invest. Derm.*, 31, 141.

In order to assess the desiccation factor separately, microbes were cultivated on pieces of callosity suspended in bottles containing H_2SO_4 variously diluted to provide differences in the vapour pressure on which the humidity of keratin is known to depend. Diphtheroids need more moisture than cocci. The effect also was studied of antibiotics and antiseptics on the growth of *Staph. aureus* in callosity suspended over 20% H_2SO_4 . J. H. T. D.

CHANGES OF THE ELECTROPHORETIC PATTERNS OF THE SERA OF PSORIATICS UNDER VARIOUS FORMS OF THERAPY. F. KALZ, J. H. QUASTEL, P. TELNER, A. SCHAFFER and W. MACINTYRE. (1958) *J. invest. Derm.*, 31, 161.

SERUM LIPOPROTEINS IN PSORIASIS. E. M. SHAPIRO, J. M. KNOX and S. GRUNDY. (1958) *J. invest. Derm.*, 31, 215.

Shapiro and Knox found no difference between psoriatics and normals, but according to Kalz *et al.* the range of γ -globulin and β -lipoprotein values in sera of 14 psoriatics examined in the Tiselius apparatus was significantly higher than in normal sera.

The serum lipoprotein level is lowered in both psoriatic and normal subjects, of whom the ages and sex are not stated, receiving daily U.V.L. exposures or intravenous injections of the chelating agent EDTA (having had its claws previously drawn for calcium). J. H. T. D.

EXPERIMENTAL CONTACT DERMATITIS. III. POISON IVY DERMATITIS IN RHESUS MONKEYS. I. ZELIGMAN. (1958) *J. invest. Derm.*, 31, 191.

Monkeys cannot, it appears from experiments performed with proprietary poison ivy extracts, be made allergic to *Rhus toxicodendron*. A contact dermatitis produced experimentally with 3-pentadecylcatechol appeared to be of the primary irritant type. The cellular reaction in the dermis resembled that of man rather than of the guinea pig. J. H. T. D.

TREATMENT OF PERSISTENT ACNE IN WOMEN WITH 17 ALPHA HYDROXYPROGESTERONE CAPROATE (DELALUTIN). A PRELIMINARY REPORT. K. C. BAKER. (1958) *J. invest. Derm.*, 31, 247.

The effect of this "esterified derivative of the naturally occurring progestational hormone" is said to last 10-14 days. It may therefore be injected on the 14th day after the last menstrual period with some prospect of influencing the endocrine state just before the next one. The improvement in the author's series of cases was not immediate; but after some months of treatment by injection once a month, in 64 of 76 women "lesions" were "controlled". (Isn't it time that we employed some sort of control standard representing the therapeutic effect of ordinary bedside manner, etc.?) J. H. T. D.

GEOMETRIC RELATIONSHIPS BETWEEN THE MATRIX OF THE HAIR BULB AND ITS DERMAL PAPILLA IN NORMAL AND ALOPECIC SCALP. E. J. VAN SCOTT and T. M. EKEL. (1958) *J. invest. Derm.*, 31, 281.

If parts of both papilla and matrix can be seen in two sections 30 μ apart it is then possible to infer from their measurements the respective volumes of the two parts of the hair bulb. Armed, with this neat little trick of geometry it is possible to judge the effect of calvities, alopecia areata, steroids and amethopterin on the hair root. J. H. T. D.

THE WAVE LENGTH EFFECT UPON ERYTHEMAL AND CARCINOGENIC RESPONSE IN PSORALEN TREATED MICE. A. C. GRIFFIN, R. E. HAKIM and J. KNOX. (1958) *J. invest. Derm.*, 31, 289.

U.V.L. between 2900 Å and 3400 Å is carcinogenic for white mice. At 2537 Å it is primarily antimicrobial. Wood's glass passes 3200-4000 Å. In this experiment a light source predominately of 2500 Å was compared with Wood's glass light containing 10% below 3200, on mice half of which had ingested or had received intraperitoneal injections of 8-methoxysporalen. The 8-MP had an important influence on the mice exposed to long wave U.V.L. J. H. T. D.

DEQUALINIUM. D. S. WILKINSON. (1959) *Practitioner*, **182**, 501.

Dequalinium, an antibacterial agent with several advantages, has recently been introduced for the treatment of skin, oral and vaginal sepsis. Under clinical conditions, dequalinium appears to bear out its experimental promise in regard to *Staphylococcus aureus* and the haemolytic streptococcus, having a powerful inhibitory effect on these pathogens. It is available in many forms, is well tolerated, does not create resistance and is cosmetically acceptable.

The main indications for use are pyococcal infections of the skin (impetigo, furunculosis), infected and infective eczematous conditions, intertrigo and mixed monilial and staphylococcal infections, staphylococcal infections of the newborn, chronic paronychia and angular cheilitis. R. J. C.

STUDIES ON MELANOMA. II. SEX AND SURVIVAL IN HUMAN MELANOMA. L. G. WHITE. (1959) *New Engl. J. Med.*, **260**, 789.

Women with melanoma survive longer than men.

A. D. P.

SKIN ERUPTIONS OF WORKERS IN A URANIUM-PROCESSING PLANT. ROY L. KILE and J. A. QUIGLEY. (1959) *Arch. Derm., Chicago*, **79**, 383.

Thanks to adequate precautions there were no eruptions due to radiation. The commonest conditions were contact dermatitis and dryness of the skin, and the usual causes were the twice daily bathing and insufficient rinsing in the laundry of underclothing issued to the workers. Other diseases were such as might be found in any group of workers. J. K.

ALOPECIA MUCINOSA. WAINE C. JOHNSON, ROBERT S. HIGDON and ELSON B. HELWIG. (1959) *Arch. Derm., Chicago*, **79**, 395.

This is a clinical and histological study of 8 cases of alopecia mucinosa, an uncommon condition which simulates parapsoriasis, or other scaly dermatosis, with alopecia. The disease may vary from a single or few lesions which heal in a matter of months to widespread lesions which tend to persist. The histopathology is characteristic, there is a change in the epithelial cells within the pilosebaceous follicle which results in the accumulation of mucin; inflammation of the corium is secondary. The authors consider that though the etiology is uncertain it is more likely to be a metabolic process than an infection as was suggested by Pinkus. J. K.

ELASTOSIS PERFORANS SERPIGINOSA. JOSEPH M. HITCH and HERBERT Z. LUND. (1959) *Arch. Derm., Chicago*, **79**, 407.

This is an account of the first cases of Miescher's elastoma reported in the U.S.A. It is remarkable that so characteristic a disease should only have been recently recognized. Has it not occurred before or has it been mistaken, for example, for granuloma annulare or Kyrle's disease? In the five cases reported the lesions occurred on the usual situation, the neck, and in young people under the age of 21. Histological examination showed marked acanthosis with the formation of penetrating epidermal pegs and reactive proliferation of connective tissue in the papillary and subpapillary layers. The pathognomonic feature is, however, a peculiar proliferation of fibres resembling elastica. These fibres penetrate the epidermis and give rise to the acanthosis. This is in contrast to Kyrle's disease which is described as a downward penetration of keratotic material into the dermis. (See also Haber's article, this Journal, **71**, 85.) J. K.

RELAXIN (RELEASIN) THERAPY IN DIFFUSE PROGRESSIVE SCLERODERMA: A PRELIMINARY REPORT. JAMES A. EVANS. (1959) *Arch. Derm., Chicago*, **79**, 159.

Relaxin is a hormone prepared from the ovaries of pregnant sows. It was administered intravenously, intramuscularly or by rectal suppository to 11 patients with generalized scleroderma. These patients were also treated by sympathectomy and diethylstilboestrol. This combined therapy brought greater flexibility of the skin in 8 of the 11 patients but there were 3 deaths including one from anaphylactoid reaction to intravenous relaxin. J. K.

IMMUNOLOGICAL ASPECTS OF HERPES SIMPLEX, HERPES ZOSTER, AND VACCINIA.

G. DOUGLAS BALDRIDGE. (1959) *Arch. Derm., Chicago*, **79**, 299.

The presence of circulating herpes antibodies is no guarantee of immunity from recurrent attacks. Repeated inoculation of smallpox vaccine reduces the incidence of outbreaks but vaccination with inactivated herpes virus has no such effect, yet the author considers that the effect of repeated smallpox vaccination is due to suggestion. The importance of avoiding trigger factors, such as exposure to sunlight, is stressed. J. K.

GAMMA GLOBULIN THERAPY IN CHRONIC STAPHYLOCOCCAL DERMATOSES. W. J. MORGINSON, DON C. WOOD and LURRINE BURGESS. (1959) *Arch. Derm., Chicago*, 79, 305.

A wide view is taken of staphylococcal dermatoses to include seborrhoeic dermatitis, intertrigo and acne. Of 170 patients 100 showed hypoglobulinaemia and of these 49 out of 59 who were given gamma globulin therapy showed satisfactory improvement. J. K.

THE TREATMENT OF DERMATOMYCOSES WITH ORALLY ADMINISTERED GRISEOFULVIN. HARVEY BLANK and FRANK ROTH, jr. (1959) *Arch. Derm., Chicago*, 79, 259.

Griseofulvin is obtained from several species of penicillium and is effective in certain plant diseases and fungal infections in animals and man. It is given by the mouth in doses of 250 mg. 4 times a day and appears to cure even such affections as small spore ringworm of the scalp in 3 to 4 weeks and ringworm of the nails in 3 to 4 months. It is not effective against monilia infections and tinea versicolor. It has a low toxicity, though urticaria and mild self limited complaints of gastro-intestinal disturbance and headache have been reported. J. K.

OBSERVATIONS ON RADIATION EXPOSURE IN DERMATOLOGICAL X-RAY THERAPY. HERBERT S. ALDEN, H. STEPHEN WEENS and HARRY D. YOUNG. (1959) *Arch. Derm., Chicago*, 79, 159.

The authors have measured the amount of radiation reaching the region of the gonads from various forms of superficial x-ray therapy. Although some radiation does reach the gonads in the use of therapeutic x-rays to the skin, the amount is well below or within the reasonable limits advised for those in the atomic industry or the general public. The authors recommend the use of cones in all treatments, the consistent and adequate use of lead shielding to the lower trunk the use of lead on or under the treatment table and the abandonment of antiquated x-ray apparatus. J. K.

ON SUDDEN OR RAPID WHITENING OF THE HAIR. ALFRED J. EPHRAIM. (1959) *Arch. Derm., Chicago*, 79, 228.

After a review of the literature the author reports a case of whitening of the hair within a week, three weeks after an accident. A strip of dark hair was left over the occiput. Subsequent tanning from sunbathing revealed patchy depigmented areas on different parts of the body. The whitening of the hair was evidently part of an acute vitiligo of the entire scalp. The mechanism of sudden change from dark to white hair is still unexplained. J. K.

DERMATOLOGICAL ASPECTS OF SARCOIDOSIS. D. G. JAMES. (1959) *Quart. J. Med.*, n.s., 28, 109.

Of 200 patients with sarcoidosis, 33 had skin lesions and a further 62 had erythema nodosum. In addition, a further 10 patients had sarcoid deposits in the skin but no evidence of generalized disease.

Kveim's tests provided histological proof of sarcoid tissue in 129 of 149 patients: they were positive in 12 of 13 patients with various skin lesions, and in 53 of 57 patients with erythema nodosum.

Nitrogen mustard, calciferol, radiotherapy, antituberculous chemotherapy and corticosteroids were used in treatment, but only the last had any beneficial effect: some improvement was noted within one week in all the 14 cases so treated.

Patients with erythema nodosum recovered without recourse to corticosteroids: hilar adenopathy subsided within 12 months of the disappearance of the skin lesions, polyarthralgia and fever. J. M. B.

RINGWORM CONTRACTED FROM CATTLE: A TWO YEARS' SURVEY IN GENERAL PRACTICE. P. T. MAIN. (1959) *Practitioner*, 182, 347.

Thirty-one cases were diagnosed during a two year period, the condition occurring chiefly in males, 90% being farmworkers or their families. The exposed sites are most commonly infected, especially the hands, wrists or forearms.

Eighty-three per cent of cases that produced a culture were found to be due to *Trichophyton discoides*.

Various treatments are discussed including zinc undecenoate ointment B.P.C., ammoniated mercury ointment B.P., Castellani's paint, Whitfield's ointment and gentian violet paint. In this study the average period of treatment was thirty-eight days, and in view of the protracted course of the disease it is important to warn the patients of this fact. R. J. C.